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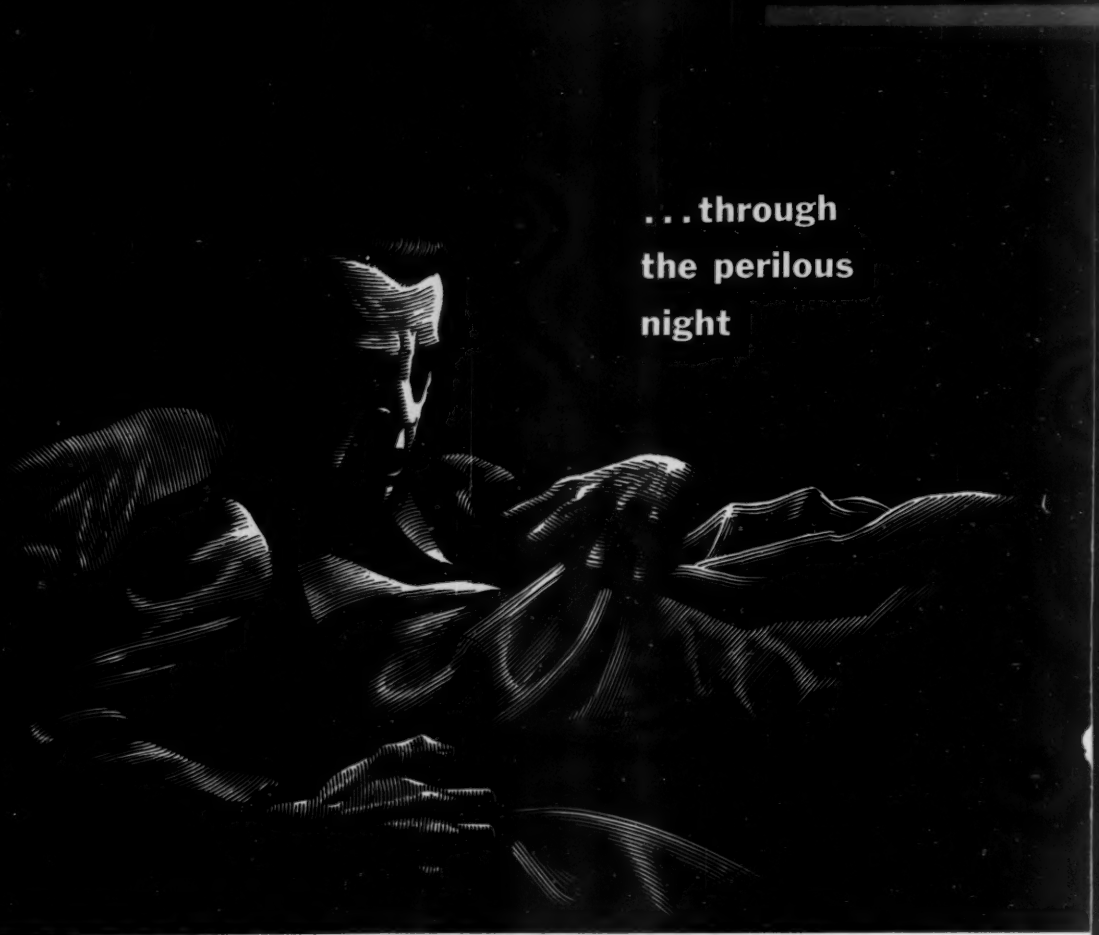

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1. Winsor, T., and Humphreys, P.: Angiology *3*:1 (Feb.) 1952. 2. Plotz, M.: New York State J. Med. 52:2012 (Aug. 15) 1952. 3. Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.

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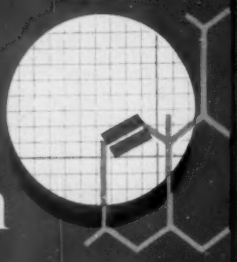

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2. Waine, H.: Bull. Rheumat. Dis. *5*:81 (Jan.) 1955.
3. Herzog, H. L., and others: Science *121*:176 (Feb. 4) 1955.

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Goodman, E.L., and Housel, E.L.: Am. J. M. Sc. 227:250 (March) 1954.

2

"There is no apparent effect on hypertension, and the drug can be used . . . in hypertensives with obesity . . . "

Finch, J.W.: J. Oklahoma M.A. 40:119.

3

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Ferguson, H. E.: Virginia M. Monthly 76:222

4

Livingston, after treating a series of 49 patients with 'Dexedrine' for 1-5 years reported that the blood pressure remained "essentially unchanged throughout the course of the treatment."

Livingston, S.; Kajdi, L., and Bridge, E.M.: J. Pediat. 32:490.

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In patients with severe hypertension, therapy should be initiated with relatively small doses and dosage increased gradually until the desired therapeutic effect is achieved.

Further Experience with Long-Term Anticoagulant Therapy

WILLIAM T. FOLEY, M.D.
ELLEN McDEVITT, M.D.
CECIL SYMONS, M.D.
and
IRVING S. WRIGHT, M.D., New York

The need for continuous administration of anticoagulants became apparent early in the clinical use of these drugs.* As a result of experience gained in the treatment of patients with rheumatic heart disease and recurrent embolization, we suggested in 1946 that these patients be maintained on anticoagulants. In 1949 our group reported on the management of 19 patients with long-term therapy.[3] Additional reports by Nichol and Fassett,[4] Cosgriff,[5] Askey and Cherry,[6] Bay and co-workers,[7] and Tulloch and Wright [8] have confirmed the favorable impression reported earlier, and the technique of long-term anticoagulant therapy is being increasingly employed. At the International Conference on Thrombosis and Embolism, at Basle, Switzerland, July, 1954, Catherine C. Burt, of Edinburgh; P. A. Owren, of Oslo; J. Dedichen, of Oslo; J. Beaumont, of Paris, and others reported similar results.

Read before the International Conference on Thrombosis and Embolism, Basle, Switzerland, July 23, 1954.

From the Department of Medicine, Vascular Section, New York Hospital-Cornell Medical Center.

Aided by grants from Mrs. Samuel Milbank, Eaton Laboratories, Inc., and the Lasker, Kress, and Hyde Foundations.

* References 1 and 2.

CLINICAL MATERIAL AND DOSAGE

The total number of patients we have followed on long-term therapy now approximates 300. This report is a summary of our experience with 85 patients who have been maintained continuously on oral anticoagulants for a minimum of one year. The length of treatment has varied from one to eight years, averaging three and a half years per patient. These patients have been followed in the Long Term Anticoagulant Clinic of the New York Hospital and in the private practices of members of the Vascular Research Group of the New York Hospital-Cornell Medical Center.

Patients with the following diagnoses were studied in this series: rheumatic heart disease with embolic episodes, recurrent thrombophlebitis with or without pulmonary emboli, and myocardial infarction. Also included were a group of patients with miscellaneous diagnoses who had thromboembolic complications.

Only those patients who could be relied upon to follow directions carefully were accepted for long-term therapy. Adequate laboratory facilities and a physician well acquainted with the problems involved were always available.

In most instances patients were already hospitalized at the time anticoagulant treatment was commenced. Where there was a need for immediate anticoagulant effect, heparin was used with ethyl biscoumacetate (Tromexan ethyl acetate) and/or bishydroxycoumarin, U. S. P. (Dicumarol). As soon as the prothrombin complex time (Link-Shapiro modification † of Quick's method [11]) reached 25 to 35 seconds, heparin was stopped. Oral anticoagulants were continued, dosage being estimated after the daily prothrombin complex time had been reported. By the time the patient was ready for discharge from the hospital it was usually necessary to determine the prothrombin complex time only once a week. As a result, the patient needed to see his physician at weekly intervals, when he was examined and careful note made of any untoward reactions. On the basis of the prothrombin complex

† References 9 and 10.

time determined at this visit, the daily dose for the following week was estimated. In some instances the patient's requirements have remained so constant that the prothrombin complex time could be determined at fortnightly intervals. One patient in this series has been tested monthly for six years. However, for ease of administration and safety, we advocate that the weekly interval be maintained.

A prothrombin complex time between 20 and 35 seconds (with a normal range of 13 to 16 seconds) was regarded as a safe therapeutic level for patients on long-term therapy. An average of 25 seconds appears ideal for most patients.

Dosage varies from patient to patient but remains fairly constant for any given patient. However, certain disturbances in physiologic balance may alter the response to the anticoagulant drug. Upper respiratory infections, diarrhea from any cause, the use of intestine-sterilizing antibiotics, low food intake, and alcoholic excess may at times reduce bishydroxycoumarin requirements, as shown by prolongation of the prothrombin time and occasionally by minor hemorrhagic manifestations.

Seventy-three of these patients were maintained on bishydroxycoumarin, and the daily dose varied from 25 to 100 mg. per day, with an approximate average of 50 mg. Ten patients received ethyl biscoumacetate, the daily dose being from 300 to 750 mg., with an approximate average dose of 600 mg. One patient was given cyclocumarol, and another phenindione (phenylindanedione).

RESULTS

Rheumatic Heart Disease.—Twenty-nine patients had rheumatic heart disease (Table 1). All had mitral valvular disease, and 26 had persistent auricular fibrillation. Twenty-five patients had had more than one thromboembolic complication before commencement of anticoagulant therapy. During a period of 765 patient-months, dating from the first thromboembolic episode to the beginning of long-term therapy, these 25 patients experienced 113 clinically recognizable episodes. Of these, 32 were pulmonary; 44, peripheral; 21, cerebral; 12, visceral, and 3, myocardial, and there was 1 episode of thrombophlebitis. While on anticoagulant therapy, a period of 1128 patient months, 7 of the 25 patients experienced 18 thromboembolic episodes. Six of these were pulmonary; three, peripheral; five, cerebral, and four, visceral in location. The remaining 18 patients had no thromboembolic episodes.

Four of the 29 patients had single thromboembolic episodes and were maintained on long-term anticoagulant therapy. During the period of 218 patient months on treatment no episodes of thromboembolism were experienced.

The following is a typical case history.

Mrs. A. J., a 43-year-old housewife, has rheumatic heart disease with mitral stenosis and insufficiency, aortic insufficiency, and auricular fibrillation. At the age of 6 years she had chorea; a heart murmur was discovered when she was 13, and at 21, during her first pregnancy, she developed cardiac failure. During the next 20 years she had recurrent episodes of failure, and, at 41, left hemiparesis developed and a diagnosis of cerebral embolism was made. The neurological condition improved rapidly, and the patient was given bishydroxycoumarin for three weeks. Seven months after this incident, evidence of gross renal infarction occurred, and, because of these two serious episodes and her persistent signs of failure, she was placed on long-term anticoagulant therapy.

She has now had 50 mg. of bishydroxycoumarin daily for 18 months, is seen at one or two weekly intervals, and is well controlled. There have been no further incidents.

TABLE 1.—*Thromboembolic Episodes in Patients with Rheumatic Heart Disease*

	Patients, No.	Not on Anticoagulant		On Anticoagulant	
		Patient-Months	Episodes, No.	Patient-Months	Episodes, No.
Two or more episodes before therapy	25	765	113	1128	18*
One episode before therapy	4	3	4	218	0

* In seven patients.

Thrombophlebitis.—Twenty-four patients, who had had recurrent thrombophlebitis during a period of 2207 patient-months, experienced a total of 92 thromboembolic episodes (Table 2). Sixty-three of these were repeated attacks of thrombophlebitis. There were 20 pulmonary emboli. Of the remaining nine, three were peripheral arterial

TABLE 2.—*Thromboembolic Episodes in Patients with Recurrent Thrombophlebitis*

Patients, No.	Not on Anticoagulant		On Anticoagulant	
	Patient-Months	Episodes, No.	Patient-Months	Episodes, No.
24	2207	92*	896	7†

* Includes 63 instances of thrombophlebitis and 20 pulmonary emboli.
† Thrombophlebitis (in 7 patients).

thrombi or emboli, two were cerebral thrombi or emboli, and there were four episodes of myocardial infarction. On anticoagulant therapy, over a period lasting 896 months, 7 of the 24 patients each had one episode of thrombophlebitis. There were no other complications.

The following case report is representative of this group.

V. J., a 50-year-old postal clerk, developed a right saphenous thrombophlebitis seven years ago, three months after a right herniorrhaphy. After six weeks of bed rest he returned to work and wore an elastic stocking until 1948, when he had a recurrence of thrombophlebitis in the same leg. In 1949, he had two episodes involving the same extremity. In 1950, he experienced a fourth attack of thrombophlebitis, accompanied by chest pain and hemoptysis, and was hospitalized. He was placed on anticoagulants and made a satisfactory recovery. Bishydroxycoumarin was discontinued, and he was discharged. Twenty-three days later, he was readmitted with a further attack of thrombophlebitis, and it was decided to keep him on long-term therapy. Three months later, after an episode of rectal bleeding, thought to be related to hemorrhoids, anticoagulants were discontinued. Three days later chest pain associated with hemoptysis developed, and bishydroxycoumarin treatment was recommended. Therapy has been continued to date, a total of 44 months. There have been no further episodes of thrombophlebitis or pulmonary embolism, and the prothrombin time is well controlled on 50 mg. of bishydroxycoumarin per day.

Myocardial Infarction.—Two groups of patients with myocardial infarction were studied (Table 3). In the first group 11 patients who had had two or more episodes of infarction were observed for 587 patient-months without anticoagulant therapy. During this time they had 49 thromboembolic episodes; 30 were myocardial infarctions; 10, pulmonary emboli; 2, peripheral; 2, cerebral; 4, visceral, and there was 1 episode of thrombophlebitis. Under anticoagulant therapy there were but three thromboembolic episodes in the subsequent period of 393 patient-months.

In the second group, 12 patients who had experienced single myocardial infarctions were treated by anticoagulants for 554 months, during which period there was one questionable thromboembolic episode.

R. M., a business executive, had a myocardial infarction eight years ago. He survived this attack and two further infarctions during the next four years. After this third episode it was considered advisable by Dr. E. S. Nichol, of Miami, Fla., to inaugurate long-term anticoagulant therapy. The patient continued satisfactorily on bishydroxycoumarin, 100 mg. per day, and saw his physician every two weeks. He was able to live a normal life and to travel about the country in pursuit of his occupation. Five years ago hematuria occurred, although the prothrombin time was within therapeutic range. Investigation revealed a renal calculus, which he later passed spontaneously, while the prothrombin time was kept at a lower therapeutic level. On a second occasion, hematuria occurred when the prothrombin time was unduly elevated. Investigation revealed that a pharmacist had refilled his prescription, giving him 100 mg. tablets of bishydroxycoumarin instead of 50 mg. tablets. His dosage was thus unwittingly doubled. A blood transfusion and intravenous vitamin K, however, quickly restored the prothrombin time to a safe level. Three months ago, while in a distant city, because of a genitourinary complaint, he discontinued bishydroxycoumarin and the prothrombin time became normal. A few days later he developed severe substernal pain and died a few hours later.

Miscellaneous.—A fourth group of nine patients was treated, comprising five with

TABLE 3.—*Thromboembolic Episodes in Patients with Myocardial Infarction*

	Patients, No.	Not on Anticoagulant		On Anticoagulant	
		Patient-Months	Episodes, No.	Patient-Months	Episodes, No.
Two or more episodes before therapy.....	11	587	49*	393	3
One episode before therapy.....	12	41	12	554	1 (?)

* Includes 30 myocardial infarcts and 10 pulmonary emboli.

TABLE 4.—*Thromboembolic Episodes in Patients with Miscellaneous Diagnoses*

Patients, No.	Not on Anticoagulant		On Anticoagulant	
	Patient-Months	Episodes, No.	Patient-Months	Episodes, No.
9*	72	20	363	3

* Five with arteriosclerotic disease, two with congenital heart disease, one with polycythemia vera, and one with multiple arterial emboli.

arteriosclerotic vascular disease, two with congenital heart disease, one with polycythemia rubra vera, and one with multiple arterial emboli from an undetermined source (Table 4). All these patients had experienced recurrent thromboembolic episodes, except for two with arteriosclerotic disease who had intractable angina and were put on long-term therapy. These nine patients were observed for 72 months prior to anticoagulant therapy, during which time they had 20 thromboembolic episodes. While on therapy for 363 months, they experienced only three episodes.

COMPLICATIONS DURING THERAPY

There were 31 hemorrhagic complications in 85 patients during 3628 months of therapy. These are shown in Table 5. In the majority of cases hemorrhage was not severe and it was only necessary to withhold the anticoagulant drug until the prothrombin-complex time had returned to a safe level. It is interesting to note, however, that in seven patients hemorrhage occurred when the prothrombin-complex time was within the therapeutic range. Further investigation in these cases revealed pathologic conditions, e. g., hemorrhoids, gynecological disorders, including one carcinoma of the uterus, and renal calculi, and bleeding was probably secondary to these abnormalities but was freer because of the anticoagulant therapy.

Vitamin K or vitamin K_1 was given on 19 occasions because the prothrombin complex time was unduly prolonged, although there was not necessarily any hemorrhage. Early in this study, synthetic vitamin K was used with good results, but its action is slow and now vitamin K_1 is the drug of choice.

Given orally, vitamin K_1 has reduced the prothrombin time to a safe level in six to eight hours. On one occasion, when hemorrhage occurred, fresh whole blood transfusion was given, but since the advent of vitamin K_1 blood transfusion is probably unnecessary, except to combat serious blood loss. Experience with vitamin K_1 is increasing. It has added greatly to the safety of anticoagulant therapy. The following dosage is tentatively suggested. If the prothrombin complex time is prolonged to a range of 50 to 90 seconds without bleeding, 10 mg. of vitamin K_1 given orally or intramuscularly will usually bring the prothrombin complex time down well towards normal within 12 hours; the first effects are noted within 3 to 4 hours. If the prothrombin complex time is more prolonged or appears resistant, additional doses in units of 10 mg. or 50 mg. may be given in one dose. If bleeding occurs the dose of 50 mg. is recommended and will usually be sufficient. The use of much larger doses will be effective, but the effects may be persistent. If the patient requires anticoagulant therapy, this may be ineffectual for some days while the vitamin K_1 is active. This is the reason for the smaller doses.

In patients who were on anticoagulants, there were very few instances of trauma causing local hemorrhage. In one patient, having intramuscular mercurial diuretics, and in another, who received penicillin, hematomas occurred.

PRESENT STATUS

The present status of the 85 patients studied is shown (Table 6). Of these, 53 are still on therapy, 14 have discontinued treat-

TABLE 5.—*Prothrombin Time Related to Hemorrhagic Complications*

	Prothrombin Time, Sec.			
	Under 25	26-40	Over 40	Unknown
Cerebral	1	..	..	..
Ecchymosis	3	2	4	4
Epistaxis	..	..	1	..
Hematuria	..	3	3	2
Hemoptysis	..	..	1	..
Melena	..	..	..	1
Rectal	..	1	..	..
Vaginal	2	1	..	2
Total	6	7	9	9

ment for various reasons, and 18 patients have died. Fifteen of these 18 patients were on anticoagulants at the time of death. The cause of death was determined clinically in 12 instances and confirmed by autopsy in 5.

CAUSES OF DEATH

In the group with rheumatic heart disease, six patients died, one from cerebral embolism, one from pulmonary embolism, three from congestive failure, and one from a cerebral hemorrhage. The last complication occurred when a patient was treated in another hospital service with Depo-Solution heparin only, without clotting time control. At autopsy it was found that hemorrhage had occurred into a cerebral infarct.

TABLE 6.—*Present Status of Eighty-Five Patients Given Long-Term Anticoagulant Therapy*

Diagnosis	Anticoagulant Continued	Anticoagulant Discontinued	Death
Rheumatic heart disease....	19	4	6*
Thrombophlebitis	14	9	1
Myocardial infarction	14	1	8*
Miscellaneous	6	0	3*
Total patients	53	14	18

* One patient in group not on drug at time of death.

In the group with thrombophlebitis, one patient died from congestive heart failure.

Eight patients died in the myocardial infarction group. Four of the eight patients of this group died from undetermined causes; three, from congestive failure, and one, from ventricular tachycardia.

Three patients in the miscellaneous group died, one after a fractured hip and two from undetermined causes.

Many of the final illnesses of patients in this series followed the pattern of the disease for which they were under treatment. Thus, congestive failure may overtake patients with rheumatic heart disease or myocardial infarction.

DISCUSSION AND CONCLUSION

There is a marked decrease in the number of thromboembolic episodes in patients with rheumatic heart disease or recurrent thrombophlebitis during anticoagulant therapy. It appears that while they are given anticoagulants the frequency of clot formation in the heart chambers and the veins is decreased, thus reducing the number of embolic accidents. Patients have tolerated this treatment well, both physically and psychologically, although in many instances their illness is severe and there is an attendant mortality from the primary disease itself. There have been few deaths in these two groups, and in only one case was it likely that an overdosage of an anticoagulant was responsible.

TABLE 7.—*Cause of Death in Eighteen Patients on Long-Term Anticoagulant Therapy*

Diagnosis				
Rheumatic Heart Disease	Thrombophlebitis	Myocardial Infarction	Miscellaneous	Cause of Death
1	..	..	..	Cerebral embolism
1	..	..	..	Cerebral hemorrhage
..	..	1	..	Ventricular tachycardia
3	1	3	..	Congestive heart failure
1*	..	..	..	Pulmonary embolism
..	..	..	1	Fractured hip
..	..	4*	2*	Undetermined

* One patient not on drug at time of death.

In assessing the results of therapy in patients who have had myocardial infarction it is necessary to study the natural history of this condition. Patients who have experienced episodes of infarction may live many years without specific treatment (Cole and co-workers [12]). Also, the condition of myocardial infarction itself does not necessarily presuppose actual thrombosis within a coronary artery. This occurs in approximately 72% of the cases. The risk from mural thrombi is nevertheless present whenever the infarction results in damage to the endothelium. The differential diagnosis cannot be

TABLE 8.—*Thromboembolic Episodes in Patients Given Long-Term Anticoagulant Therapy*

Patients, No.	Not on Anticoagulant		On Anticoagulant	
	Patient-Months	Episodes, No.	Patient-Months	Episodes, No.
85	3673	290	3552	32

made with certainty during life. Long-term anticoagulants are indicated when recurrent infarction has taken place, when episodes of failure are prominent, and when multiple embolic accidents have occurred. Lastly, long-term anticoagulants have been used in certain instances in which myocardial infarction seemed impending, in the hope that under protection of therapy, which may prevent or defer future infarctions, collateral circulation in the myocardium may continue to develop and thus minimize damage to the heart muscle. No such cases are included in this study.

This experience indicates that anticoagulant therapy may be safely employed for long periods, provided the treatment is conducted carefully and conscientiously by both the physician and the patient. The course of certain diseases complicated by thromboembolic episodes may be favorably altered.

SUMMARY

Eighty-five patients with disease characterized by thromboembolic episodes were placed on long-term anticoagulant therapy, from periods of one to eight years—a total of 3552 patient-months.

Patients with the following diagnoses were treated: rheumatic heart disease, recurrent thrombophlebitis, myocardial infarction, and certain diseases with miscellaneous diagnoses.

Thirty-one hemorrhagic episodes occurred, the majority of which were mild. One patient died after a cerebral hemorrhage.

Eight-five patients, selected as outlined above, observed for a total of 3673 patient-months without anticoagulants, had 290 thromboembolic episodes. During a period of 3552 patient months on anticoagulant therapy, these same patients experienced 32 thromboembolic complications.

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Abnormalities of Body Water, Sodium, Potassium, and Magnesium

Pathogenesis, Clinical Manifestations, and Treatment

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I. CLASSIFICATION

The classification of abnormalities of water volume and/or sodium concentration is presented in Table 1.[1] From the standpoint of pathogenesis, the abnormalities may be divided into two groups: (*a*) conditions characterized by a primary alteration in extracellular volume or sodium concentration and a secondary shift of water between interstitial tissue and cells to effect equilibrium of osmotic pressure;* (*b*) conditions characterized by a primary cellular disturbance, with alteration in the content or concentration of osmotically active intracellular electrolytes and a parallel change in the osmolarity of the extracellular compartment. The pathogenesis and clinical manifestations of these two groups are presented separately.

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* The principal clinical terminology for primary abnormalities in extracellular volume and sodium concentration is indicated by asterisks in Table 1.

TABLE 1.—*Classification of Abnormalities of the Content and Distribution of Water and Sodium*

	Hyponatremic Syndromes (Decreased Plasma Na Concentration)	Isonatremic Syndromes (Normal Plasma Na Concentration)	Hypernatremic Syndromes (Increased Plasma Na Concentration)
Deficit of water	Hypotonic dehydration* or "salt depletion"	Isonatremic dehydration	Hypertonic dehydration* or water depletion or "hyperosmolar syndrome"
	Extracellular osmolarity relative less than osmolarity of cell†	Extracellular osmolarity normal and equal to osmolarity of cell	Extracellular osmolarity greater than osmolarity of cell
Normal hydration	Asymptomatic hyponatremia Extracellular osmolarity decreased but equal to osmolarity of cell	Physiologic state	Asymptomatic hypernatremia Extracellular and cell osmolarity both equally increased
Excess of water	"Water intoxication"* Extracellular osmolarity less than osmolarity of cell; marked secondary increase in intracellular fluid	Isonatremic edema	Hypertonic edema
	Hyponatremic edema Extracellular osmolarity decreased but equal to osmolarity of cell	Extracellular osmolarity normal and equal to osmolarity of cell	Extracellular and cell osmolarity both equally increased
	"Low salt syndrome" Extracellular osmolarity less than the lowered cellular osmolarity		

* Principal clinical terminology for primary abnormalities in extracellular volume and sodium concentration.

† It is also possible to have hyponatremic dehydration, wherein extracellular osmolarity is low but equal to cell osmolarity.

II. PATHOGENESIS OF PRIMARY ABNORMALITIES

Pathogenesis of primary abnormalities of water volume and sodium concentration is given in Table 2.† The basic predisposing factor in the dehydration syndrome is fluid loss.‡ If losses continue unchecked, the syndrome likely to develop will depend partly upon the osmolarity of the fluid lost from the body. The consequence of unrequited loss of hypotonic fluid (*e. g.,* sweat in acclimated persons, coupled with evaporation from the skin and lungs) is hypertonic dehydration.§ The immediate effect of loss of isotonic fluid (*e. g.,* from gross hemorrhage or extravasated plasma) is isonatremic dehydration.‖ This is a temporary state, with symptoms and signs referable more to salt depletion; its subsequent course depends upon therapy.

Isonatremic dehydration may pass into either hypertonic or hypotonic dehydration,¶ depending upon whether the process of adjustment leaves the patient in relative water or sodium depletion. The former ensues when the correction is inadequate chiefly in water; the latter, when it is inadequate principally in sodium. Water intoxication # may be superimposed upon loss of isotonic fluid when water is forced, in a misguided therapeutic effort.

The mistakes that precipitate the syndromes of hypertonic or hypotonic dehydration and water intoxication represent errors in the volume and/or sodium concentration of the intake that cannot be compensated by

TABLE 2.—*Pathogenesis of Primary Abnormalities of Body Water Volume and/or Sodium Concentration*

	Hypotonic Dehydration	Water Intoxication	Hypertonic Dehydration
A. Fluid Lost, Source and Electrolyte Concentration	**Syndrome Predisposed if Losses Continue Unchecked**		
Blood, isotonic	Hemorrhage	Abnormal losses of isotonic fluid predispose by causing sodium depletion; syndrome is actually precipitated by the erroneous administration of excessive water	.....
Plasma, isotonic	Extravasation of plasma		
Gastric secretion, isotonic	Vomiting, gastric suction		.....
Intestinal secretions, isotonic	Diarrhea, intestinal suction		
Urine, variable tonicity	Relatively high Na content		Relatively low Na content
(*a*) Renal disease	(*a*) Chronic pyelonephritis		(*a*) Polyuria with low Na
(*b*) Endocrine disease	(*b*) Addison's disease; diabetic acidosis		(*b*) Diabetes insipidus; diabetic glycosuria
(*c*) CNS disease	(*c*) Salt wasting, increased intracranial pressure		(*c*) Water wasting, frontal lobe lesion
Skin, very hypotonic	.....	.....	Sweat in acclimated persons
Lungs, electrolyte-free			Insensible perspiration
B. Intake Incorrect in Volume and/or Na Concentration	**Syndrome Precipitated if Intake Is Grossly Erroneous**		
Sodium intake	Na intake inadequate to correct deficit Erroneous use of water or glucose solutions instead of electrolyte solutions		Sodium excess exaggerated by "physiologic" saline or other isotonic electrolytes
Water intake	Inadequate volume because of CNS depression and lack of thirst	Excessive owing to unbridled thirst or injudicious administration of glucose in water	Inadequate to correct dehydration because of CNS distortion and lack of thirst
C. Excretory Compensation Inadequate	**Syndrome Aggravated if Selective Excretory Adjustment Cannot Be Made**		
	Hypotonic Dehydration	Water Intoxication	Hypertonic Dehydration
Renal adjustment impaired	Decreased capacity to conserve Na and H_2O	Decreased capacity to conserve Na	Decreased capacity to excrete Na
(*a*) Renal disease		Decreased capacity to excrete H_2O	Decreased capacity to conserve H_2O
(*b*) Decreased renal blood flow			
(*c*) Renal functional impairment			
Hormonal abnormalities			
Hydrocortisone and/or aldosterone	If decreased	If decreased	If increased
Antidiuretic hormone		If increased	If decreased

† References 1-5.

‡ References 6-8.

§ References 9-16.

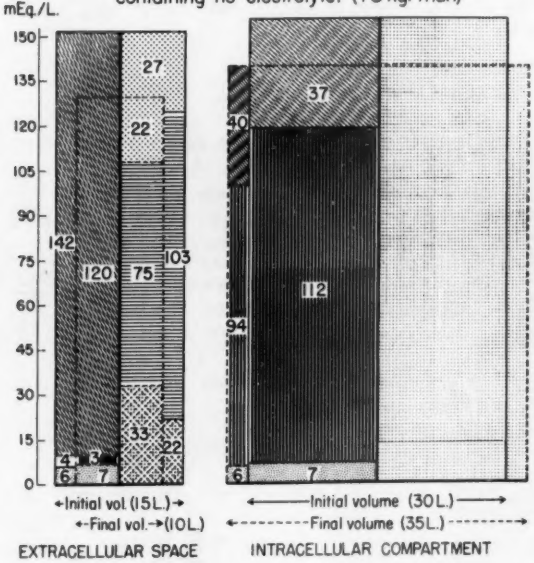
‖References 6-8.

¶ References 17-19.

References 20-24.

excretory adjustment. In the replacement of current losses, the use of "physiologic" saline or another fluid isotonic in sodium will provide abundant sodium but not enough water for the excretion of the high sodium intake and will, therefore, precipitate hyperosmolarity. In the treatment of dehydration, the administration of water or 5% glucose in water will aggravate hypotonicity if the intake is too small to restore volume or will precipitate water intoxication if the intake is excessive. The modified Gamble diagram,[25] Figure 1, illustrates the hypothetical production of hypotonicity by (1) loss of half of all gastrointestinal secretions for a period of 48 hours; (2) erroneous replacement by an identical volume of solution containing no electrolyte. Figure 2 is constructed in the same fashion, to exemplify the experimental production of hypertonicity by (1) losses of body fluid, including considerable hypotonic perspiration; (2) erroneous replacement by an identical volume of "physiologic" saline. Even when the water and sodium content of the extracellular compartment are originally normal, forcing of water above the capacity

Alterations in volume and electrolyte concentration in extracellular and intracellular compartments resulting from loss of half of G.I. secretions for 2 days and replacement by an equal volume of 5% glucose in water containing no electrolyte. (75 kg. man)



WATER AND ELECTROLYTE BALANCE

	ml.	mEq.			
	H_2O	Na	K	Cl	HC_3
Gastric j.	2500	50	40	360	
Bile	500	70	3	55	20
Pancr. j.	700	100	4	30	75
Succus ent.	3000	420	18	330	90
Insensible persp.	1800				
Urine	500	10	35	15	
TOTAL LOSS	9000	650	100	790	185
INTAKE:					
Glucose in water	9000				

Na HCO_3
K Cl A
Ca + Mg. R

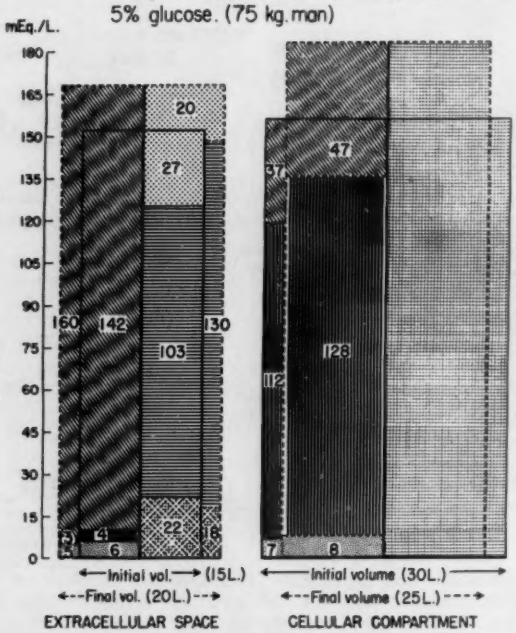
Fig. 1.—The volumes of the extracellular and intracellular compartments are depicted on the abscissas; the concentration of cations and anions, on the ordinates. The normal findings are indicated by solid columns; the alterations that would be expected after a substantial loss of body fluid, together with an erroneous effort at replacement with 5% glucose in water, are represented by broken columns. The normal volumes in the diagram slightly exceed the actual figures found by radioisotope techniques; the electrolyte concentrations represent averages and thus do not conform to the actual values for any given tissue. In the hypothetical patient, the lost body fluid amounted to 900 ml. and was approximately half isotonic in sodium; the 5% glucose in water used for replacement corresponded to the volume lost but furnished no sodium. The resultant sodium depletion and water replacement diluted the extracellular compartment to reduce its osmolarity below that of the cells. To compensate for this disparity, there was prompt shift of a large amount of water, accompanied by a relatively small amount of sodium, from the interstitial spaces into the cells. As a consequence, there was a significant reduction of extracellular space, an expansion of the cells, a decrease in plasma sodium concentration, and an equalization of tonicity on the two sides of the cell membrane. If there had been insufficient water to restore depletion, hypotonic dehydration would have resulted; if water intake had been excessive, water intoxication might have been precipitated.

for excretion may precipitate water intoxication, whereas the forcing of "physiologic" saline may result in hyperosmolarity, even in the absence of dehydration.

When renal function is normal and the loss or excess intake of water or electrolyte is not too great, protection from the loss may be afforded by renal conservation, whereas compensation for excess intake may be achieved by increased excretion through the kidneys and other channels. The evaluation of the capacity of excretory adjustment to compensate for losses of water and/or sodium or for errors in intake necessitates a review of idiorenal and hormonal factors concerned in the conservation or elimination of water and sodium.

In the normal man, the average plasma flow through the sum total of glomeruli (Figure 3) is 900 liters per 24 hours, each liter containing 140 mEq. sodium and 60 gm. protein (assuming a protein concentration of 6 gm./100 cc.). Filtered into the composite proximal convoluted tubules, there is a total of approximately 180 liters per 24 hours, containing 140 mEq. sodium per liter but only minute quantities of protein. Of the filtrate in the proximal convoluted tubules,

Alterations in volume and electrolyte concentration in extracellular and intracellular compartments resulting from loss of hypotonic sweat for 3 days and replacement by an equal volume of isotonic saline containing 5% glucose. (75 kg. man)



WATER AND ELECTROLYTE BALANCE

	ml.	mEq.			
	H_2O	Na	K	Cl	HCO_3
Sweat	4000	100	60	160	
Insensible persp.	3600				
Urine	1200	85	80	110	
Stool	200	15	20	25	10
TOTAL LOSS	9000	200	160	295	10
INTAKE					
5% Glucose in saline	9000	1350		1350	
		+	−	+	−
NET	0	1130	160	1055	10

Na HCO_3
K Cl A
Ca + Mg. R

Fig. 2.—The method of the diagram is similar to that of Figure 1. The normal findings are indicated by solid columns; the alterations that would be expected after a substantial fluid loss together with an ill-conceived effort at replacement with "physiologic" saline are represented by broken arrows. The hypothetical balance data show similarity in volumes lost and replaced, but there is a great excess of sodium in the isotonic repair solution over that in the very hypotonic excreta. This disparity was accentuated by continuing elimination of relatively greater quantities of water than of sodium. The resultant rise in plasma sodium level increased the osmolarity of the extracellular compartment above that of the cells. To compensate for this disparity, there was a prompt shift of a large amount of water from the cells into the interstitial space. As a consequence, there was a significant contraction of the cells, expansion of the interstitial spaces, and an equalization of osmotic pressure on the two sides of the cell membrane. A primary excess of sodium and inadequacy of water constitute hypertonic dehydration; a primary elevation of sodium with normal to increased extracellular volume, but with cellular dehydration, constitutes hyperosmolarity.

approximately 150 liters, containing 140 mEq. sodium per liter, return to the capillaries by passive (obligatory) reabsorption, even in the absence of hormonal effects (Fig. 3). This leaves approximately 30 liters of isotonic sodium concentration to enter the distal convoluted tubules; part of this residue is reabsorbed through idiorenal factors that can operate independently of hormonal action. In the distal tubular epithelium, conversion of carbon dioxide and water into carbonic acid, and thus into hydrogen and bicarbonate ions, is facilitated by carbonic anhydrase; deamination of glutamine to form ammonia is accomplished by glutaminase (Fig. 3). Through interchange with hydrogen ions, some sodium ions are reabsorbed from the tubular lumen and move thence into the capillary along with bicarbonate, thereby reducing the sodium content of the urine. Part of the hydrogen is excreted as such or by conversion of Na_2HPO_4 into NaH_2PO_4; part is neutralized by the action of ammonia. Additional sodium is conserved by interchange with potassium. Since water is reabsorbed along with sodium, the urine is reduced in volume, even in the absence of hormonal action. Interference with these mechanisms by drugs such as carbonic anhydrase inhibitors or by disease, such as pyelonephritis, reduces the reabsorption of sodium and water and leads to a diuresis of both substances (Fig. 4).

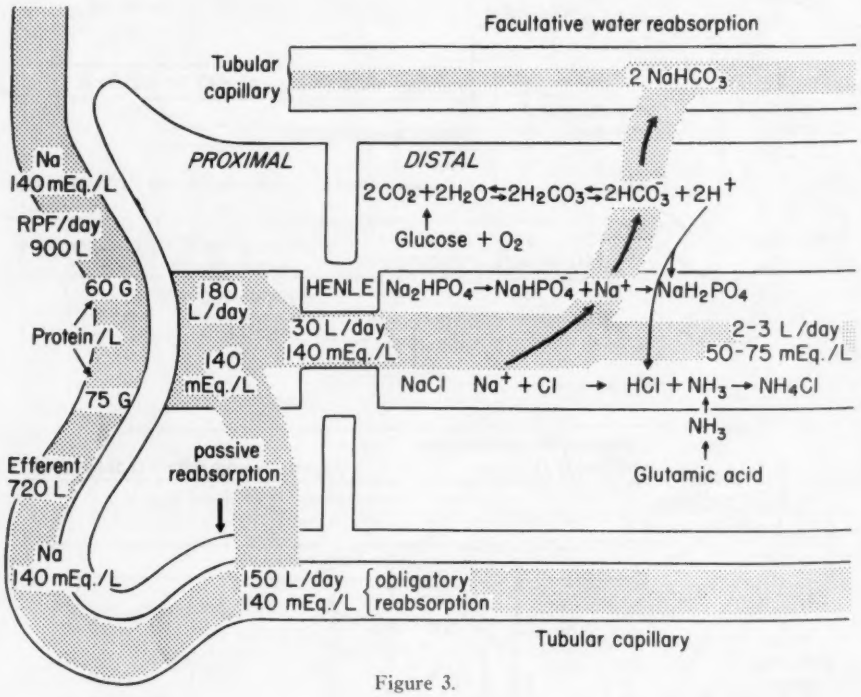
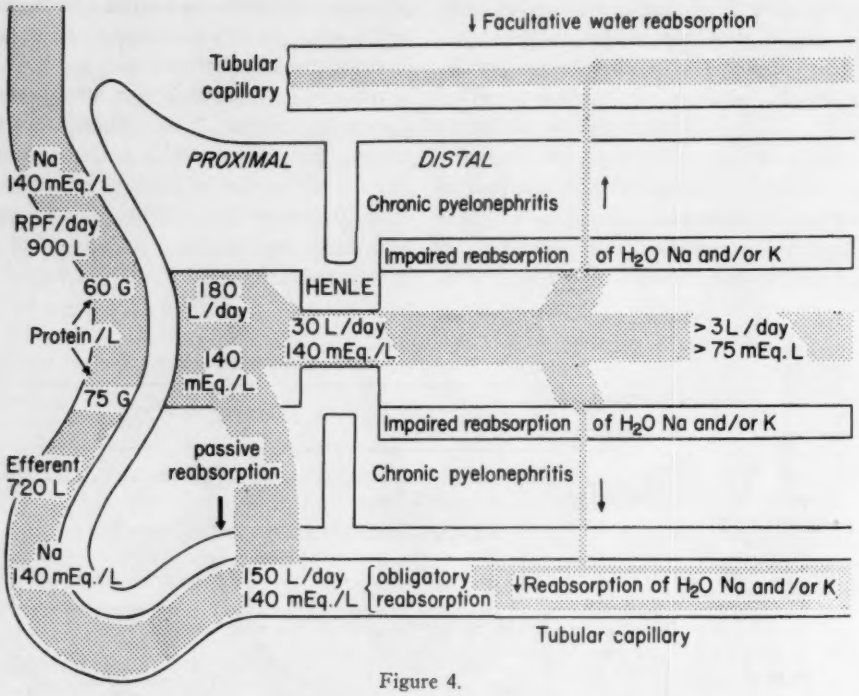


Figure 3.

In normal persons, there is a measurable blood level of 11,17-oxycorticoids, the largest active fraction of which consists of hydrocortisone (F), the next largest, corticosterone (B).* The effect of these agents is to increase the reabsorption of sodium, particularly in the distal but also in the proximal convoluted tubules, and to facilitate an exchange of potassium, which escapes in increased amounts in the urine (Fig. 5).[28] The blood level of 11,17-oxycorticoids is normally

* References 26 and 27.



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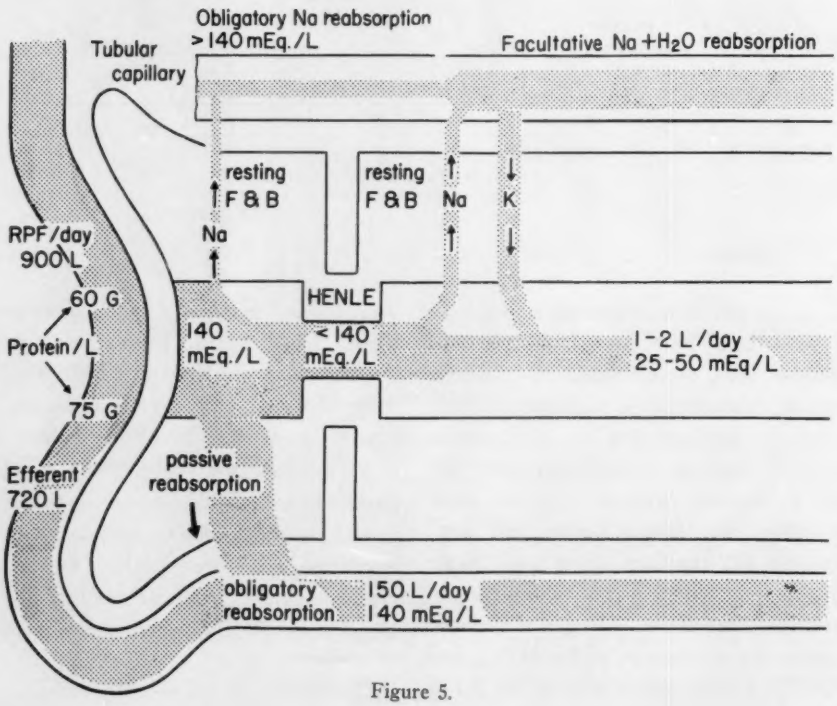

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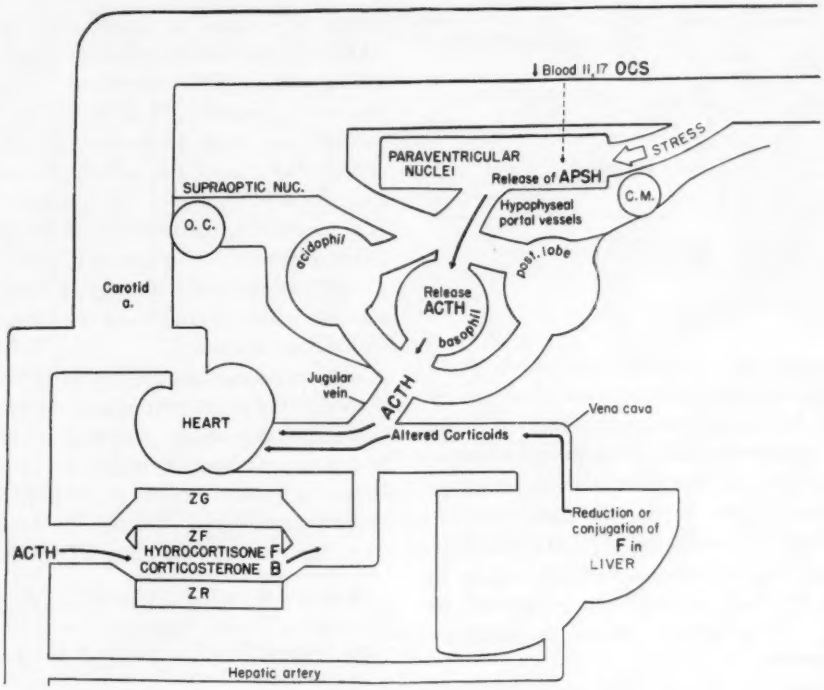

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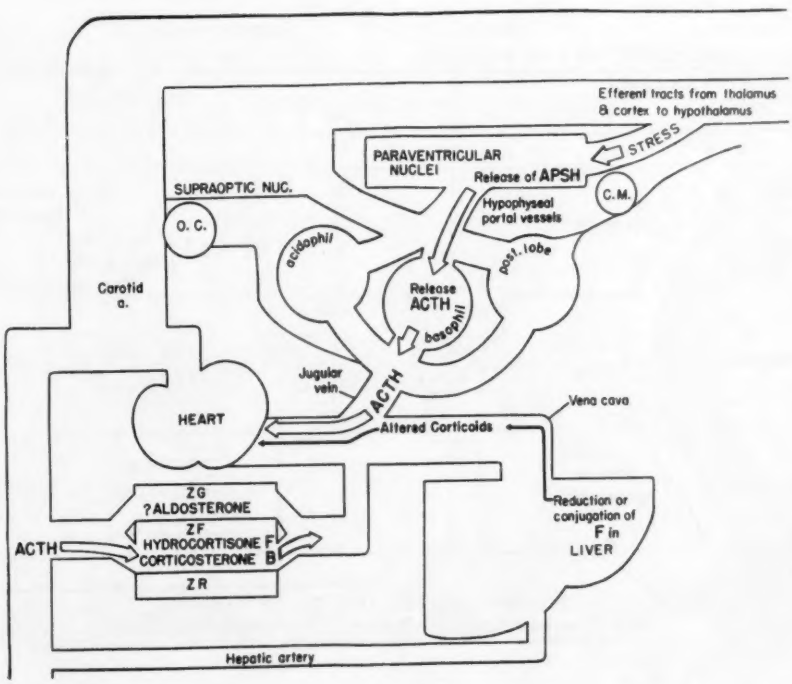


Figure 7.

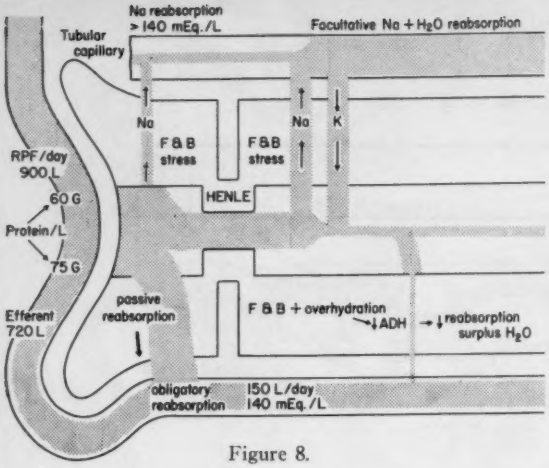


Figure 8.

maintained by a humoral mechanism that is analogous to thermostatic control in the sense that a fall in the blood concentration in animals apparently leads to an increased output and a rise, to a diminished release. Although the mechanism is as yet undetermined, the available evidence suggests regulation through the hypothalamus.† A fall in the blood 11,17-oxycorticoid concentration is believed to stimulate certain hypothalamic nuclei to release a lipoprotein hormone (APSH) into the hypophyseal portal circulation, whence it is carried to the anterior lobe of the pituitary (Fig. 6).‡ APSH apparently acts upon certain anterior lobe cells, presumably basophiles, which, in turn, release corticotropin into the general circulation. Circulating corticotropin is concentrated in the adrenals within a minute and prompts the elaboration and discharge of hydrocortisone and corticosterone into the adrenal vein within two minutes.§

The increased amounts of hydrocortisone needed in the event of traumatic or emotional stress are apparently produced in response to neurogenic stimuli, which evoke the release of a greater amount of APSH from the hypothalamus ‖ and, thus, more corticotropin from the anterior lobe (Fig. 7). Although a

† Hume, D. M., and Wittenstein, G. J.: The Relationship of the Hypothalamus to Pituitary-Adrenocortical Function, in Mote,[29] p. 134.

‡ Hume, D. M., and Wittenstein, G. J.: The Relationship of the Hypothalamus to Pituitary-Adrenocortical Function, in Mote,[29] p. 134.

§ References 30 and 31.

‖ Hume, D. M., and Wittenstein, G. J.: The Relationship of the Hypothalamus to Pituitary-Adrenocortical Function, in Mote,[29] p. 134.

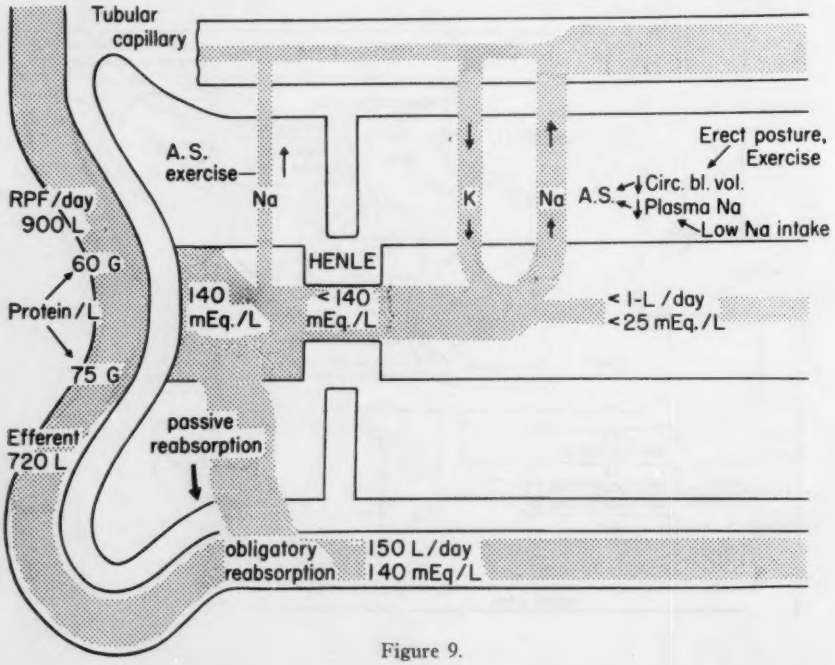


Figure 9.

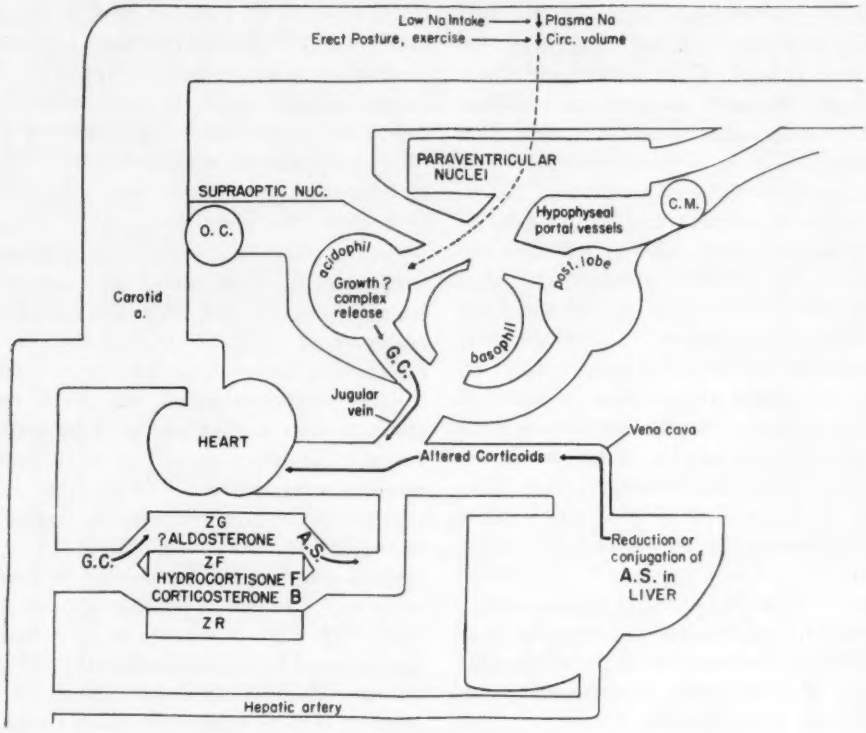


Figure 10.

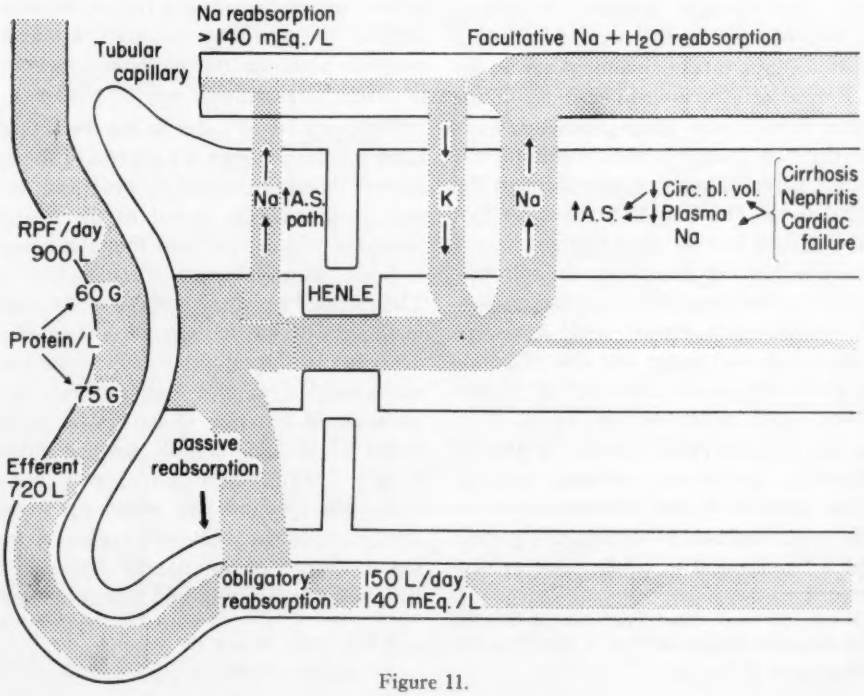


Figure 11.

portion of the increased corticoids liberated by the adrenals is inactivated in the liver and elsewhere (Fig. 7),¶ the blood level is still increased sufficiently to exert an enhanced effect upon the renal tubules (Fig. 8). This is manifested by an increased reabsorption of sodium and excretion of potassium. Excessive output of adrenal corticoids in Cushing's syndrome also causes sodium retention and potassium loss; absence in Addison's disease leads to excessive losses of sodium and water and thus to dehydration. Sodium retention is ordinarily accompanied by a parallel increase in tubular reabsorption of water to maintain normal extracellular osmolarity. On the other hand, surplus water, as in the Robinson-Power-Kepler test, is promptly excreted in the presence of adequate or excessive hydrocortisone but is retained in the presence of Addison's disease.[28] The tubular rejection of surplus water in the presence of adequate hydrocortisone may possibly be attributable to suppression of the endogenous release of aldosterone (electrocortin) and antidiuretic hormone (Fig. 8).

In the normal person, when the plasma sodium concentration and/or circulating blood volume tend to fall, as a result of a minimal sodium intake, maintenance in an erect instead of a recumbent posture, or indulgence in exrcise in place of sedentary activity, there is conservation of sodium and water by increased reabsorption through the renal tubules.# This may be attributable to a relatively slight increase in the production of aldosterone,[34] either directly in the adrenals or by conversion from corticosterone. Aldosterone causes much greater renal reabsorption of sodium and water and loss of potassium than comparable amounts of hydrocortisone and corticosterone (Fig. 9).[35] Although the data are at present in need of confirmation, preliminary evidence suggests that the adrenals secrete aldosterone in response to a constituent of the pituitary growth complex [36] instead of in response to corticotropin (Fig. 10).[37] Pituitary growth complex may possibly be released through a humoral mechanism, as represented in Figure 8. Although aldosterone is, in part, reduced or conjugated in the liver,[37] slight increases that presumably occur in response to low-salt diet, erect posture, and exercise have renal effects, as indicated in Figure 9.

In congestive failure, cirrhosis, and nephrosis, there is an augmented conservatism of body sodium, not only by increased tubular reabsorption (Fig. 11)[38] but also by diminished secretion through other channels.* Tubular reabsorption of sodium in these states is even further increased by maintenance of an erect instead of a recumbent posture or by indulgence in exercise. The exaggerated sodium retention in congestive failure, cirrhosis, and nephrosis is due to increased aldosterone,[34] which may be evoked by increased release of pituitary growth complex (Fig. 12). Conservation of sodium is accompanied by retention of water and thus edema. This occurs chronically in the absence of clinical manifestations of Cushing's syndrome. If the preliminary data on aldosterone are confirmed and this hypothesis is verified, the profound influence of this hormone on abnormalities of sodium concentration and water volume will be obvious.

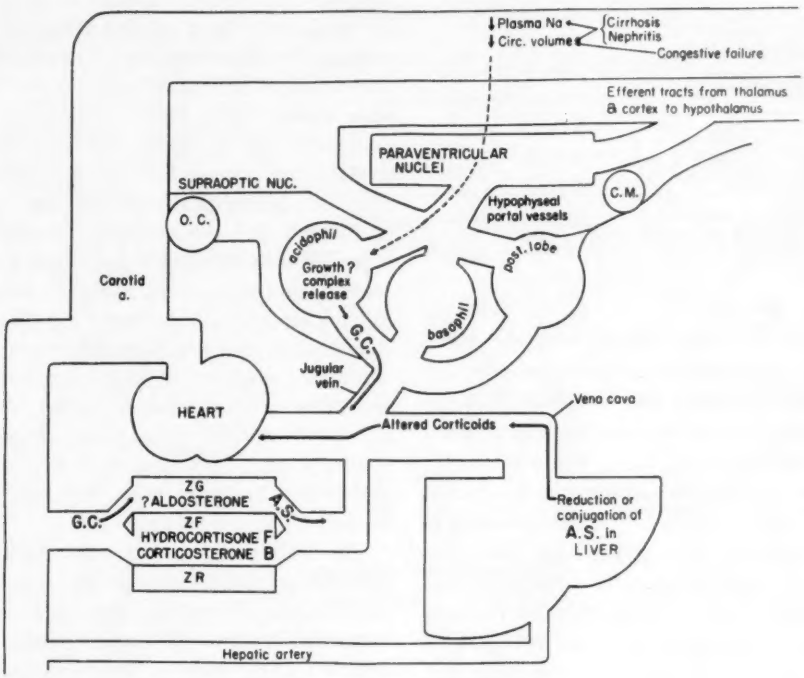
Reabsorption of water in the distal convoluted tubules is under the control of the antidiuretic hormone, which is produced in the supraoptic nucleus, stored in the neurohypophysis, and release into the circulation in response to appropriate stimuli (Fig. 13). The cardinal activator is a rise of osmolarity in the plasma of the hypophyseal capillaries over that in the receptive cells of the supraoptic nucleus, as was demonstrated by the intracarotid injection of hypertonic saline.[41] Other physiologic stimuli, such as primary sodium retention and/or reduction in circulating blood volume and emotion,† presumably act upon the supraoptic nucleus to evoke the discharge of antidiuretic hormone into the infundibular stalk and thence its release

¶ Mason, H. L.: Urinary Excretion of Steroids During Administration of ACTH, in Mote,[29] p. 168.

References 32 and 33.

* References 39 and 40.

† References 41-44.



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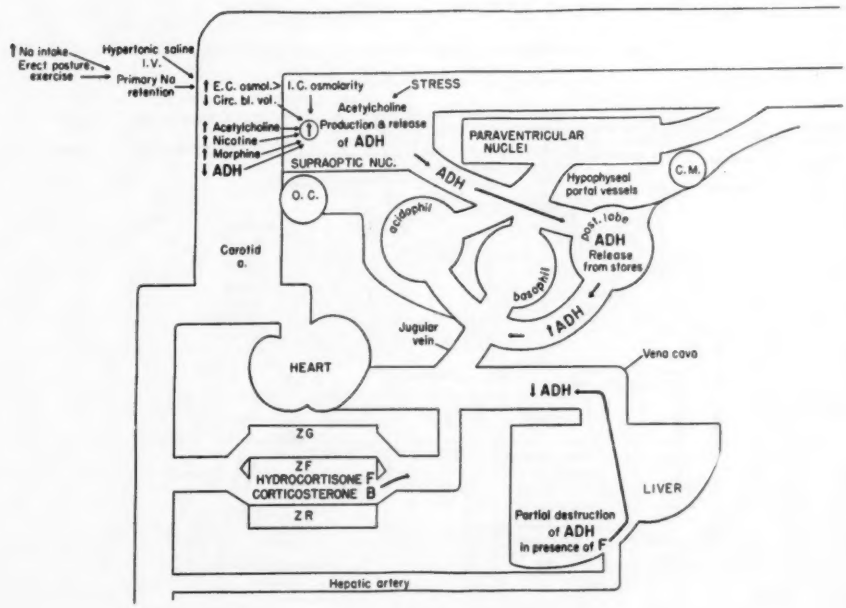

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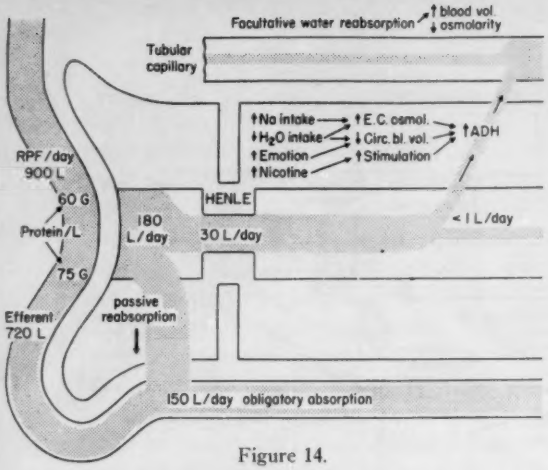


Figure 14.

from the neurohypophysis into the blood stream. Pharmacologic agents such as acetylcholine, nicotine, and morphine [45] stimulate the supraoptic nucleus to produce comparable effects (Fig. 13). A portion of the secreted antidiuretic hormone is inactivated in the liver,[46] particularly in the presence of hydrocortisone, but physiologic quantities reach the distal convoluted tubules to promote water reabsorption, thereby reducing the urinary volume, as indicated in Figure 14. More rigorous stimulation of the supraoptic nucleus, as a result of exaggerated sodium retention or circulatory collapse, may evoke a maximal release of antidiuretic hormone (Figure 15)‡ and a maximal antidiuresis in the distal convoluted tubules (Fig. 16). The release of ferritin from the liver in shock may contribute to the stimulation of the supraoptic nucleus (Fig. 15).[45]

A fall in the osmolarity or rise in the volume of the plasma bathing the supraoptic nucleus physiologically checks the normal production and release of antidiuretic hormone (Fig. 17) and thus interferes with the reabsorption of water in the distal convoluted tubules, leading to a diuresis (Fig. 18).§ Alcohol causes pharmacologic depression of the supraoptic nucleus and elicits a greater diuresis than an equal volume of water. Destruction of the supraoptic nucleus and posterior pituitary stops production and release of antidiuretic hormone (Fig. 19) and results in diabetes insipidus (Fig. 20).

The sodium and water content of the body is thus regulated physiologically by excretory adjustments effected through idiorenal and hormonal factors. Hormonal excess or insufficiency aggravates or produces abnormalities in sodium and water metabolism.

‡ References 47-50.
§ References 41-44.

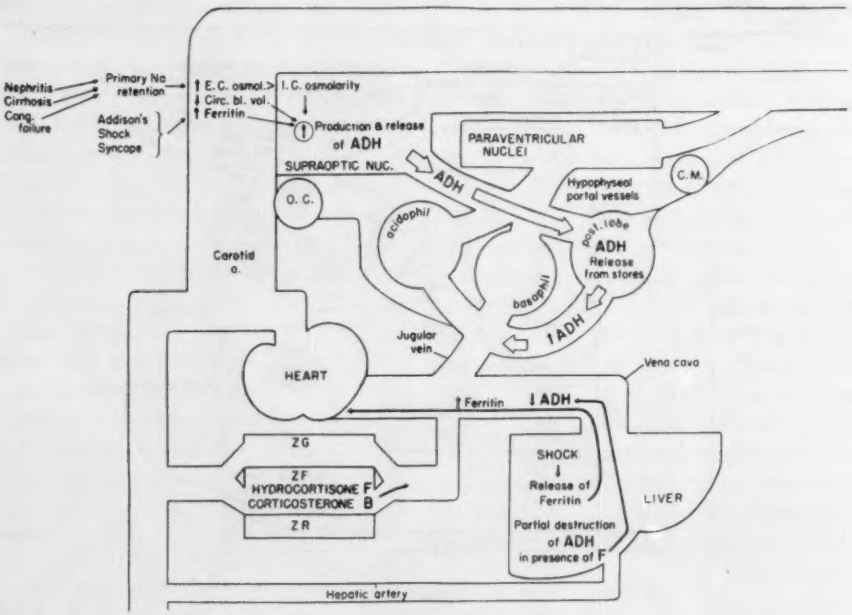
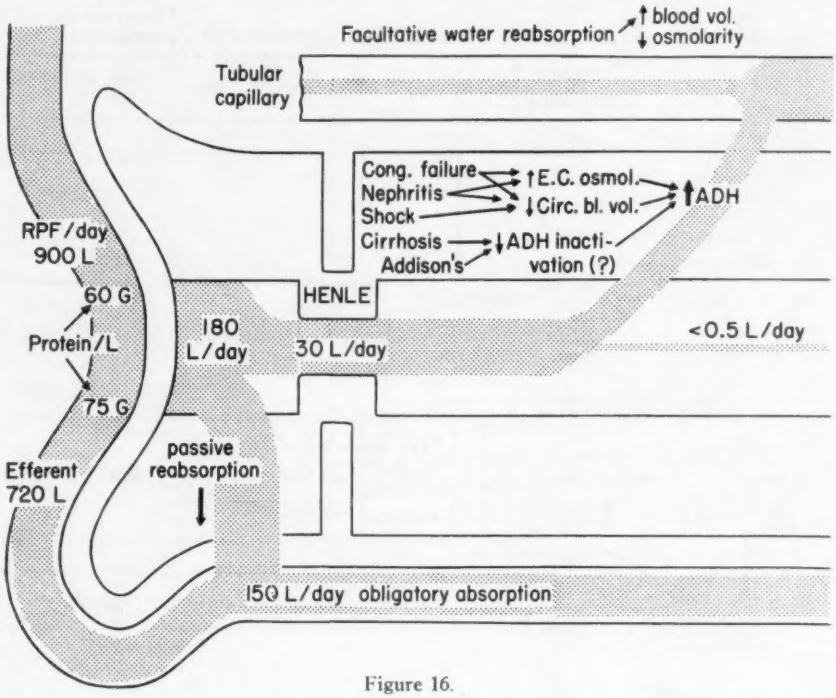


Figure 15.



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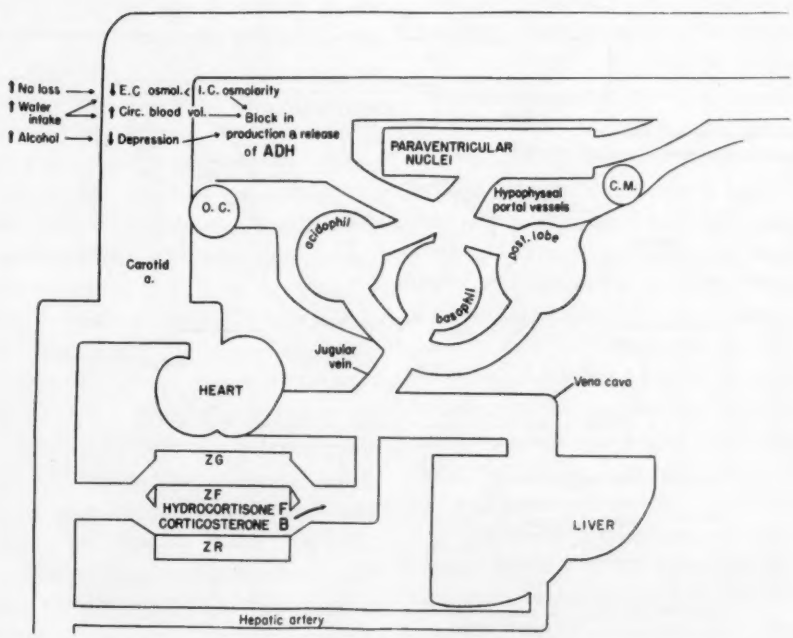


Figure 17.

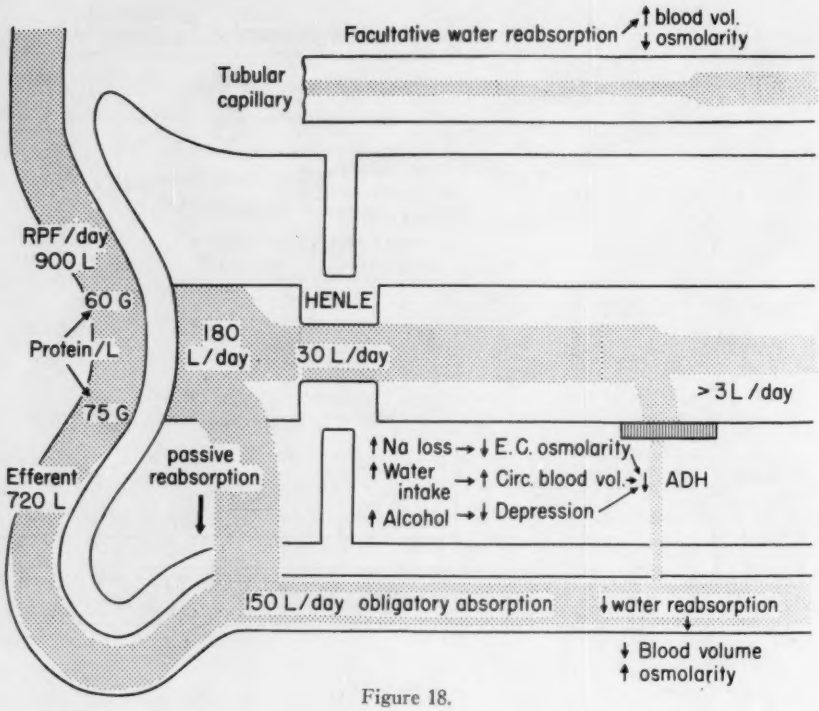


Figure 18.

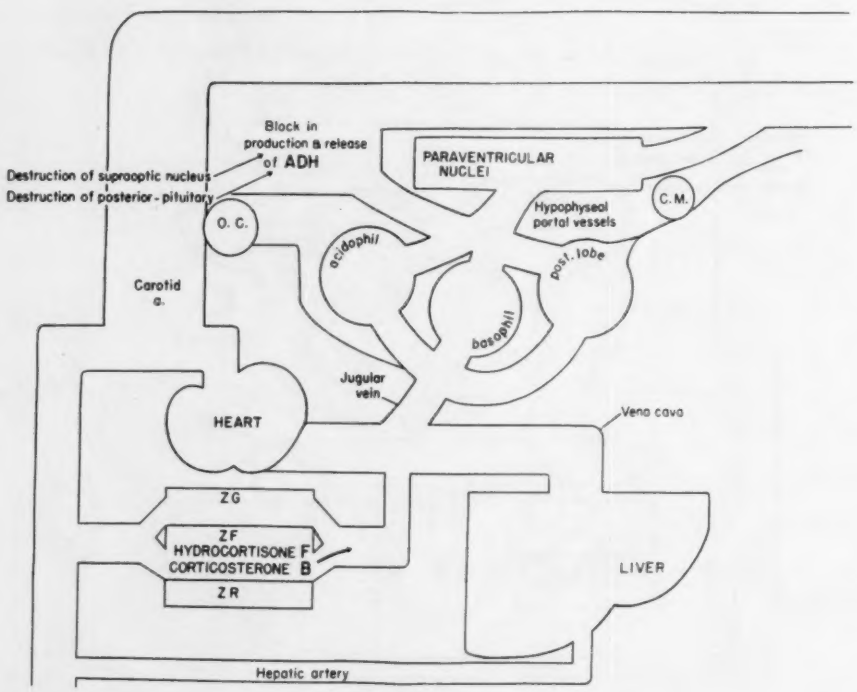


Figure 19.

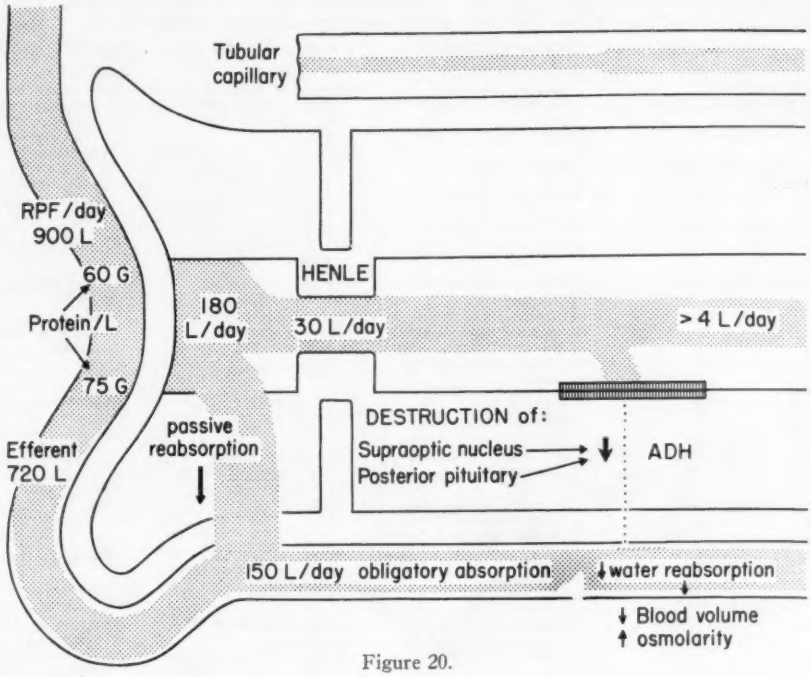


Figure 20.

III. CLINICAL MANIFESTATIONS OF PRIMARY ABNORMALITIES

Clinical manifestations of primary abnormalities of water volume and sodium concentration || are listed in Table 3. The diagnosis is greatly facilitated by accurate data on the volume and electrolyte concentration of the previous output and intake; in the absence of accurate data, estimates are helpful. In hypotonic dehydration the predominant cerebral manifestations are those of depression from reduced blood flow; in water intoxication they consist of increased intracranial pressure from edema; in hypertonic dehydration they comprise distorted accuracy from focal lesions. Weight is decreased and there is dryness of skin and mucous membranes in both forms of dehydration; weight is increased in water intoxication, and there is a tendency to cutaneous edema, that yields finger prints on the patient's forehead.[1] In hypertonic dehydration, the clinical manifestations are referable to cellular dehydration, but the volume of the extracellular compartment is also subnormal. In other cases of primary hypernatremia, sufficient extracellular water may be present to bring the extracellular volume up to or above normal; in these cases, clinical manifestations are likewise present and are referable entirely to cellular dehydration. Primary hypernatremic states with cellular dehydration are collectively referred to as the hyperosmolar syndrome. Cramps on muscular contraction are associated with both hyponatremic states but not with hypernatremia. In hypotonic dehydration the blood volume is reduced, the hematocrit value is increased, and the blood sodium is low; in water intoxication the blood volume is increased, the hematocrit value is reduced, and the blood sodium is very low; in the hyperosmolar syndrome the volume and hematocrit value will be dependent upon the volume of water shifted out of the cells, but the sodium concentration is elevated.

|| References 1-5.

TABLE 3.—*Clinical Manifestations of Primary Abnormalities of Water Volume and Sodium Concentration*

	Hypotonic Dehydration	Water Intoxication	Hypertonic Dehydration
	Cerebral depression	Cerebral edema	Distorted accuracy
Nervous system			
Early functional abnormalities	Apathy, lassitude, headache, drowsiness	Headache, disorientation, violent behavior	Irritability, restlessness, abnormal behavior, confusion, hallucinations, dysarthria
Late functional abnormalities	Stupor → coma	Convulsions, muscle twitching, ataxia, focal lesions (e. g., paralysis, aphasia), papilledema, projectile vomiting, delirium, mania → coma	Focal lesions, hyperpnea, hyperthermia, dilirium, mania → coma
Gastrointestinal tract	Intake inadequate and improper	Increased extrarenal water excretion	Intake inadequate and improper
	Anorexia, dry mouth, lack of thirst and savour, nausea, vomiting, atony, pylorospasm	Salivation, vomiting Watery diarrhea	Anorexia, no thirst, owing to CNS distortion
General appearance	Dehydration	Water retention	Dehydration
Weight	Weight ↓; haggard, sallow	Weight ↑	Weight ↓
Skin	Dry, loose, wrinkled, inelastic	Cutaneous edema, yielding finger prints on patient's forehead	Dry, flushed
Mucous membranes	Dry; tongue shrunken with longitudinal wrinkling	Moist	Dry, red, may be swollen
Muscles	Weak, putty-like, fatigable, cramps on contraction	Weak, fatigable, cramps on contraction	Weak, no cramps
Cardiovascular state			
Early	Exertional dyspnea, orthostatic hypotension, tachycardia	Heart normal, B. P. normal Pulse normal, respirations may be ↑ or ↓	Hyperpnea → terminal respiratory paralysis Hypotension → peripheral circulatory collapse
Late	Heart sounds distant; circulatory collapse Supine hypotension; pulse feeble Cutaneous blood flow ↓; veins collapsed	Cardiac function maintained B. P. may be ↑, pulse may be ↓ Capillary circulation normal; veins full	
Blood			
Volume	Volume decreased; hematocrit increased	Volume increased; hematocrit decreased	Volume may be increased
Protein	Concentration increased; total decreased	Concentration decreased	Concentration decreased
Na, Cl concentration	Low	Very low	Elevated
Potassium concentration	May be elevated	Lowered	May be decreased
Urine			
Output	Volume decreased; S. G. increased	Volume usually decreased; S. G. decreased	At first increased, then decreased
Sodium concentration	Decreased except in renal or Addison's disease	Decreased except in Addison's or renal disease	Should be increased, but may not be

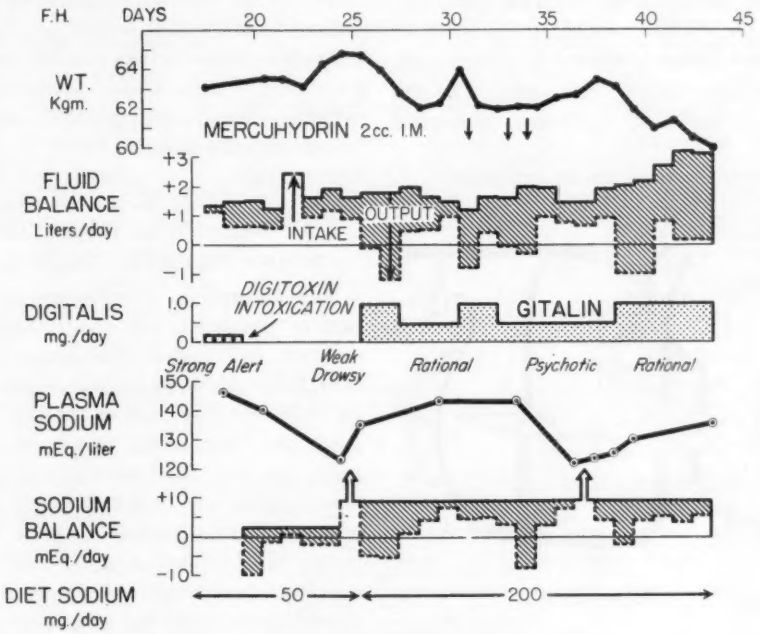
IV. PATHOGENESIS AND MANIFESTATIONS OF SECONDARY ABNORMALITIES IN EXTRACELLULAR VOLUME AND SODIUM CONCENTRATIONS

The primary abnormality is presumably a cellular disturbance, altering the content or concentration of osmotically active intracellular electrolytes. As a secondary manifestation, there is a parallel change in the osmolarity of the extracellular compartment. Deviations can occur in both directions and are discussed separately.

A. Hyponatremic Syndromes.—Either of two syndromes, asymptomatic hyponatremia ¶ or hyponatremic edema,[54] may be associated with chronic debilitating disease. In each, there is apparently a primary depletion of cellular protein, accompanied by release, extrusion, and excretion of its associated electrolyte, and a concomitant fall in plasma sodium concentration to maintain parallelism in osmolarity. Asymptomatic hyponatremia is encountered particularly in pulmonary and

¶ References 51-53.

meningeal tuberculosis; hyponatremic edema develops as a complication of cirrhosis and malnutrition, from nephrosis and congestive failure, from relatively great loss of sodium through the overuse of mercurials with or without retention of water, or from dietary errors or endogenous production of antidiuretic hormone (ADH).[54] These syndromes are suspected in the presence of underlying malnutrition, hypoalbuminemia, and edema. As the name implies, asymptomatic hyponatremia is recognized by the lack of clinical manifestations, the preservation of extracellular volume, and the lowering in sodium concentration. Hyponatremic edema is accompanied by a refractory increase in extracellular volume and lowering in sodium concentration, but it is otherwise asymptomatic.



Refractory congestive heart failure due to rheumatic heart disease

Fig. 21.—The patient had rheumatic mitral, tricuspid, and aortic stenosis and insufficiency and was in severe congestive failure that had been refractory to bed rest, low-sodium diet, diuretics, and digitoxin in doses that produced clinical and electrocardiographic evidence of toxicity. The chart was begun towards the end of digitoxin administration, just after symptoms of water intoxication had been temporarily controlled by hypertonic saline. In the graphs of fluid and sodium intake and output, positive balances are present when the lower margin of the shading is above zero; negative, when below zero. Concomitant with the presence of digitoxin intoxication before and after its withdrawal, there was significant retention of water, as shown by the positive balance and the rising weight, but there was a slight negative balance of sodium, probably attributable to the rigid 50 mg. intake. This led to a progressive drop of plasma sodium concentration from 146 mEq. to 122 mEq. per liter, at which level symptoms of cerebral edema appeared. A single injection of hypertonic saline relieved symptoms and increased plasma sodium by 10 mEq. per liter. Meanwhile, the sodium intake was increased to 200 mg. daily and treatment with gitalin (amorphous) was instituted. During initial dosage of 1.0 mg. daily, diuresis of water and sodium occurred and the plasma sodium rose to normal levels; after reduction of the dose to 0.5 mg., water and sodium retention recurred and prompted readministration of meralluride, U. S. P. (Mercuhydrin). The retention of relatively more water than sodium caused an abrupt fall in plasma sodium concentration to 120 mEq. per liter and precipitated a psychosis with prominent delusions of reference and persecution. Another intravenous injection of hypertonic saline gave prompt symptomatic relief but did not alter the plasma sodium concentration significantly. With resumption of a 1 mg. daily dose of gitalin, there was a gradual fall in weight and rise in sodium concentration, associated with water diuresis but a slight retention of sodium.

Patients with either of the foregoing hyponatremic syndromes are particularly susceptible to additional acute loss of sodium or excessive intake of water and are prone to develop one of the following clinically manifest complications: "low salt syndrome" or water intoxication. Low-salt syndrome [55] is manifested by cerebral depression, anorexia, muscular asthenia and cramps, oliguria, and azotemia, as in the salt-depletion syndrome, but differs in respect to interstitial fluid volumes. In the low-salt syndrome residual subcutaneous hypotonic edema is present, although weight may be decreasing, whereas in the salt-depletion syndrome interstitial fluid is reduced sufficiently to give clinical signs of dehydration. Water intoxication may develop from the indiscriminate administration of water or glucose solutions to a patient whose capacity to eliminate excessive water is impaired because of cardiac failure, renal disease, adrenal insufficiency, or increased endogenous antidiuretic hormone. The cardiac patient is likely to retain acute water loads when inadequately digitalized. Patients in chronic cardiac failure may exhibit concomitant gain in weight and fall in plasma sodium concentration; a water diuresis may occur in response to digitalization by adequate doses of the same preparation or by substitution of a glycoside with a higher therapeutic ratio (Fig. 21).

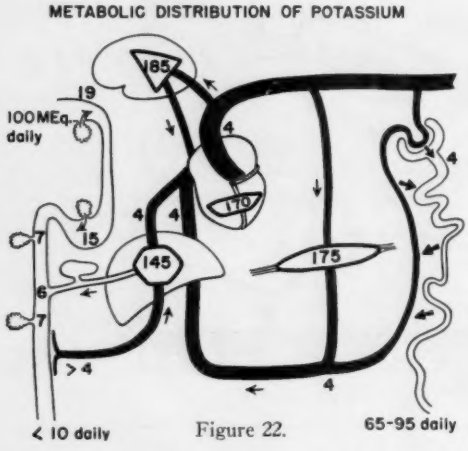


Figure 22.

B. Hypernatremic Syndromes.—The opposite type of primary cellular disturbance, namely, conversion of inert, protein-bound intracellular electrolyte into osmotically active ions, would appear to occur particularly in congestive failure # before therapeutic modifications lead to one of two syndromes, asymptomatic hypernatremia or hypertonic edema. To keep the extracellular osmolarity parallel with the rising intracellular tonicity, there is a simultaneous tubular retention of sodium, leading to an increase in plasma concentration. Hypernatremia with normal extracellular volume is asymptomatic; hypernatremic edema is accompanied by an increase in extracellular volume, but it is otherwise asymptomatic.

V. PATHOGENESIS OF ABNORMALITIES IN PLASMA POTASSIUM CONCENTRATION

The absorption, distribution, and excretion of potassium are illustrated diagrammatically in Figure 22; the factors leading to hyperkaliemia and hypokaliemia are classified in Table 4.* The normal diet is liberal in potassium, containing approximately 100 mEq. per day. Nevertheless, the concentration of potassium in the plasma is kept normally within the narrow range of 3.5 to 5.0 mEq./liter (average, 4 mEq./liter), and elevation to toxic levels in the interstitial space is prevented by cellular uptake of potassium and by renal excretion of surplus (Fig. 22). The latter is accomplished by rejection of filtered potassium and, when necessary, by tubular secretion. Surplus potassium in the diet and potassium salts, given orally in therapeutic doses, are adequately handled by the normal patient. The intravenous infusion of potassium salts in concentrated solutions at a rapid rate will produce hyperkaliemia, even in the normal subject. In patients with marked reduction in glomerular filtration rate, as in renal disease manifested by anuria or severe oliguria, a normal or lowered potassium intake will lead to hyperkaliemia (Table 4). As will be discussed below, the hyper-

References 56-59.

* References 62-65.

kaliemia of lower nephron nephrosis is due not only to the markedly reduced glomerular filtration rate but also to the inability of the damaged tubules to secrete potassium and their failure to prevent reabsorption of potassium from the lumen back into the blood. The more frequent error of intake is the exclusive use of parenteral feedings containing no potassium supplement. This is a common mistake, particularly in the vomiting and postoperative patient; it leads to depletion of body potassium and ultimately to hypokaliemia. Even though potassium intake is inadequate, excretion through the urine, stools, and vomitus continues and is responsible for the depletion. When there are rapid changes in extracellular volume without concomitant adjustment in potassium content, the plasma potassium concentration may be significantly altered. An abrupt dehydration is accompanied by hyperkaliemia; overhydration, by hypokaliemia.

The most important single factor governing plasma potassium is the capacity of the kidneys to compensate and thereby keep the plasma concentration within normal range.

TABLE 4.—*Pathogenesis of Abnormalities in Plasma Potassium Concentration*

Hyperkaliemia		Hypokaliemia
Excessive	← Intake →	Inadequate
1. Rapid i. v. infusion of concentrated solutions of potassium salts 2. Administration of normal diet to patients with marked oliguria		1. Exclusive use of parenteral feedings containing no potassium supplements
Dehydration	← Rapid changes in extracellular volume →	Expansion
Inadequate	← Excretion →	Excessive
1. Renal manifestations A. Anuria or severe oliguria B. Excessive tubular reabsorption of K (1) Inadequate adrenal steroids (*a*) Insufficient hydrocortisone and corticosterone (1) Addison's disease (2) Adrenogenital syndrome with complicating Addison's disease (*b*) Insufficient aldosterone		1. Renal manifestations A. Polyuria B. Inadequate tubular reabsorption of K (1) Excessive adrenal steroids (*a*) Cushing's syndrome (*b*) Primary aldosterone (2) Tubular damage (*a*) Chronic pyelonephritis (*b*) Lower nephron nephrosis 2. Extrarenal manifestations A. Gastric (repeated vomiting, gastric suction) B. Intestinal (severe diarrhea, intestinal suction)
Retention in plasma in event of marked depression of GFR and anuria due to	Abnormal shift of K ← from cells to plasma → due to	Immediate excretion of potassium transferred to plasma in event of normal renal function with depletion of tissue stores and ultimate hypokaliemia aggravated by failure to replenish potassium
1. Accompanying shock 2. Accompanying dehydration 3. Underlying renal disease	1. Tissue anoxia (*a*) Traumatic shock (*b*) Medical shock (*c*) Cardiac failure 2. Tissue breakdown (*a*) Protein catabolism (*b*) Glycogenolysis 3. Metabolic acidosis (*a*) Severe diarrhea (*b*) Excessive acid intake (*c*) Excessive production (1) Diabetic acidosis (2) Starvation 4. Metabolic alkalosis (*a*) Repeated vomiting (*b*) Alkali ingestion	1. Treatment of alkalosis exclusively with parenteral glucose, NaCl or NH_4Cl 2. Treatment of acidosis exclusively with parenteral glucose, sodium chloride, bicarbonate or lactate
	Abnormal shift of K from plasma to cells	1. Avidity of recovering tissues for K, used for (*a*) Replenishment of deficit (*b*) Protein anabolism (*c*) Glycogenesis 2. Periodic family paralysis

Hyperkaliemia of renal origin (Table 4) is the result of either (1) marked reduction in glomerular filtration rate, manifested clinically by anuria or severe oliguria; (2) inability of some damaged tubules to protect against hyperkaliemia by secretion of potassium or by refusal to reabsorb it from the lumen; (3) inability of even normal tubules, in the presence of Addison's disease, to protect against excessive reabsorption of potas-

sium (Table 4). Hypokaliemia may be a complication of polyuria, since even the normal kidney is unable to conserve potassium adequately in the presence of somatic depletion; it is commoner in association with the polyuria of pyelonephritis, since some damaged tubules have reduced capacity to make adjustments by reabsorption of potassium. Excessive exogenous or endogenous adrenal corticoids, as in iatrogenic hypercorticism, Cushing's syndrome, and primary aldosteronism,† also lead to urinary wastage of potassium, even in the presence of normal kidneys, and to reduction in tissue and ultimately plasma potassium levels. Hypokaliemia also results from loss of potassium through other channels, notably the upper gastrointestinal tract, by vomiting and gastric suction, and the lower gastrointestinal tract, by diarrhea and intestinal suction (Table 4). The total losses of potassium may be great, since saliva and gastric juice ordinarily contain 15 to 20 mEq. potassium per liter and bile, pancreatic juice, and succus entericus contain 5 to 7.5 mEq. per liter.

The plasma potassium concentration may deviate beyond normal range because of abnormal shifts between the extracellular and intracellular compartments. The normal maintenance of a low plasma and high intracellular concentration (Fig. 22) is achieved by the selectivity of an intact cell membrane. Damage to the cell membrane, as a result of anoxia (shock, cardiac failure), or excessive tissue breakdown with protein or glycogen catabolism result in the transfer of cellular potassium to the plasma (Table 4). The resultant plasma concentration will be governed by the capacity of the kidneys to make immediate adjustment. Hyperkaliemia will ensue if there is oliguria due to accompanying shock, dehydration, or underlying renal disease. On the other hand, normal renal function permits immediate excretion of the potassium transferred to the plasma and maintains normal extracellular levels for the time being but progressively depletes the stores and leads ultimately to hypokaliemia. A concomitant intake inadequate in potassium does not compensate for losses and hastens the advent of hypokaliemia. Metabolic acidosis accelerates the loss of cellular potassium, since it provokes the transfer of additional amounts into the plasma to accompany the increased anions into the urine. Metabolic alkalosis leads to cellular uptake of sodium, which displaces potassium out to the extracellular compartment; if the excess potassium is excreted, hypokaliemia is the ultimate sequel. Alkalosis per se also induces greater renal loss of potassium because of reduced amounts of competing hydrogen ions in the tubular cells. The potassium deficit in acidosis and alkalosis is likely to be aggravated by the inability of the patient to take adequate amounts by mouth and by the use of parenteral solutions containing little or no potassium.

During recovery of depleted tissues, protein anabolism and glycogenesis necessitate increased cellular uptake of potassium. Recovering tissues exhibit an avidity for potassium and replenish deficits, even at the expense of reducing the plasma concentration below the normal range. Clinically manifest and even fatal hypokaliemia may occur during recovery from diabetic coma, etc., for the foregoing reasons. In periodic family paralysis there is a periodic shift of plasma potassium into the muscles, resulting in hypokaliemia that is responsible for the clinical manifestations.

VI. CLINICAL MANIFESTATIONS OF ABNORMALITIES IN PLASMA POTASSIUM CONCENTRATION

(Table V)

There may be relatively little difference in the symptomatology of hyperkaliemia and hypokaliemia, as is evident from Table 5.‡ The nature of the deviation in plasma potassium level can usually be determined at the bedside, provided that there is reliable information regarding the underlying illness and the approximate potassium intake and output. Deviations of clinical significance can be recognized and evaluated by electrocardiogram; the distinctive electrocardiographic

† References 60 and 61.

‡ References 62-65.

features of hyperkaliemia and hypokaliemia are described in Table 5. Whenever possible, the diagnostic survey should include a determination of plasma potassium level to supplement the electrocardiographic findings and to detect deviations that had produced no changes.

VII. PATHOGENESIS OF ABNORMALITIES IN MAGNESIUM METABOLISM

The normal diet furnishes about 30 mEq. magnesium daily,[66] approximately twice the minimal requirement.[67] The serum magnesium concentration is normally 1.60 ± 0.14 mEq./liter §; elevation to the toxic range has not been reported from overeating per se but can be produced by oral supplements or parenteral injection of magnesium salts, particularly in patients with renal insufficiency.

§ Serum magnesium is increased by parathyroid hormone; the nondiffusable fraction, which normally constitutes approximately 15% of the total, is increased by thyroid hormone.[67]

TABLE 5.—*Clinical Manifestations of Abnormalities of Blood Potassium*

	Hyperkaliemia	Hypokaliemia
Neurological and mental	Listlessness, apathy, mental confusion, heaviness of legs, weakness, hypotonia, and terminal flaccid paralysis	
	Paresthesia common	Paresthesia rare
		Gasping (fish mouth) breathing
	Nausea and vomiting	
Gastrointestinal		Atonic abdominal distension, paralytic ileus
Cardiovascular	Cold gray pallor	Cyanosis
	Low pulse pressure, bradycardia	Wide pulse pressure, collapsing pulse
	Faint heart sounds	Functional systolic murmurs
	Peripheral circulatory collapse	Cardiac dilatation and failure
	Sudden death from cardiac arrest	
Genitourinary	Often oliguria and azotemia	Often preexistent polyuria
ECG	The electrocardiographic changes associated with clinical potassium excess can be correlated fairly well with the extracellular concentration of potassium, and so the word hyperpotassemia can be used without reservation; comparable T waves may be recorded in acute subepicardial injury with normal blood potassium, presumably as a result of local extrusion of intracellular potassium; electrocardiographic changes due to hyperpotassemia are enhanced by a concomitant lowering of plasma sodium and calcium levels	The electrocardiographic changes associated with clinical potassium deficiency are probably correlated better with a low intracellular concentration of potassium, which may or may not be reflected in the serum potassium level; the word hypopotassemia here is taken to mean a state of potassium deficiency which produces electrocardiographic changes
	ST segment, T wave, and U wave	
	All normally upright T waves become characteristically church-steeple-like in contour as plasma K rises above 6.5-7.0 mEq/L.; the upright T wave of hyperkaliemia has a narrow base, steep concave ascending and descending limbs, and a tall pointed peak; inverted T waves of cavity origin (e. g., aV_R become deeper and resemble the mirror-image of the upright T waves; abnormally inverted T waves in leads from the epicardium of either ventricle may become less inverted and often upright	ST junction shows progressive depression in leads with a predominant R wave. The ST segment sags downward from the depressed ST junction in a U-shaped curve to end in a low upright to inverted T; concurrently the U wave becomes increasingly exaggerated as one or more humps, to result in a double camel back or a triple rolling contour; the U wave tends to fuse with the T wave, so that measurements of the QT interval are likely to be made to the end of the U wave and to thus appear erroneously prolonged; although fused in some leads, the T and U waves are usually distinctive in other leads, which are utilized for measurements
	QRS complex	
	Characteristic changes in the T wave precede alterations in QRS; the first change in QRS occurs with levels in the vicinity of 8 mEq/L. and consists in increase in amplitude and duration of S wave in left precordial leads at the expense of the R; with levels of 9-11 mEq/L., intraventricular block of the RBBB type develops, and with still higher levels defective intraventricular conduction progresses to the point of cardiac arrest; preterminally the QRST is fused into an unusually broad smooth biphasic sinuous curve	Usually no change; occasionally slight widening may be observed
	P wave and PR interval	
	P wave decreased in amplitude and increases in duration up to the point of sinoauricular block and arrest of auricular activity at high potassium levels; there is a resultant shift to a ventricular pacemaker; this is at first regular, but with increasing hyperkaliemia ventricular fibrillation may occur	PR interval may be slightly prolonged

Urinary excretion during therapeutic infusions depends upon the serum magnesium level and the glomerular filtration rate. The absolute amount reabsorbed by the tubules is relatively constant. Whether or not tubular reabsorption is regulated by hormonal activity is unknown. Thus far, tubular secretion of this ion has not been demonstrated.

Hypomagnesemia has not as yet been reported from qualitative inadequacy of the food; however, in the presence of a history of dietary insufficiency over a prolonged period, acute deprivation of magnesium, as in parenterally fed alcoholic, cirrhotic, or postoperative patients, can apparently precipitate clinical manifestations. Continued urinary excretion contributes to the magnesium depletion; hypomagnesemia must be watched for, particularly when urinary wastage may be excessive, as in the recovery stage from acute renal failure, the polyuric phase of chronic pyelonephritis, or overuse of ammonium chloride and mercurial diuretics. Elimination through the gastrointestinal tract also contributes to magnesium depletion, since approximately 60% of the magnesium excreted from the body is recovered from the feces [68]; however, hypomagnesemia has not as yet been reported exclusively from vomiting or diarrhea, despite the fact that diarrheal stools contain 100% of magnesium ingested.[69]

The intracellular concentration of magnesium is relatively high, approximately 30 to 45 mEq. per liter of cellular water. Most of intracellular magnesium probably exists in un-ionized combinations with protein; it apparently plays an important role in protein and carbohydrate metabolism, bone formation, and neuromuscular conduction. During the development of diabetic acidosis, significant losses of magnesium have been found, but elevation of blood level is possible if there is coexistent renal insufficiency. Rapid shift of magnesium into the cells, along with potassium, contributes to the hypomagnesemia encountered during recovery from diabetic coma.[70] Patients with severe diabetes, but no ketosis, may have low magnesium levels, probably as a result of the disturbed carbohydrate metabolism.[71] Hypomagnesemia accompanying pancreatitis is presumably due to precipitation of magnesium salts of fatty acids.

VIII. CLINICAL MANIFESTATIONS OF ABNORMALITIES OF BLOOD MAGNESIUM

Hypomagnesemia may be accompanied by muscular tremors and twitching, athetoid and choreiform movements, convulsions, delirium, confusion, disorientation, and coma, according to some workers || but not all.[70] Although there is some correlation between the severity of the manifestations and the magnesium concentration, not all patients with hypomagnesemia exhibit these symptoms. Apparently, frank tetany is not a common finding.[74]

Although elevation of serum magnesium is frequently seen in renal failure, hypermagnesemia of toxic degree has been described only in association with parenteral or oral administration of magnesium salts. Toxic manifestations progress from loss of deep tendon reflex through suppression of respiration to inhibition of cardiac function, as the serum magnesium level increases from 6 mEq. to 12 mEq. per liter.

IX. TREATMENT OF ABNORMALITIES OF BODY WATER AND ELECTROLYTE CONCENTRATIONS

When the patient is first seen, the therapist has two problems: (1) correction of the initial status in respect to water content and electrolyte concentrations and (2) provision of water and electrolyte to replenish losses predicted for the next 24 hours. Separate estimates of corrective and replenishment solutions are made daily, as described in the ensuing outline, and are customarily combined to make a sum total for administration over the next 24 hours. Although solutions required for correction of hypotonic dehydration may be hypertonic, solutions for replenishment of losses predicted during the next 24 hours are always hypotonic, owing to the fact that they cover losses of electrolyte-free insensible perspiration, hypotonic sweat, and dilute urine; consequently, the sum total is usually hypo-

|| References 72 and 73.

tonic.¶ These estimates are made each morning; modifications may be necessary in the late afternoon, on the basis of clinical observations or laboratory reports of studies performed during the day. If the patient, after restoration of normal hydration, is still unable to adjust water and electrolyte excretion in accordance with needs (as in persistent anuria), the therapist should continue to prescribe intake for each future 24-hour period, on the basis of predicted losses.

A. Hypotonic Dehydration.—1. Correction of Initial Status in Respect to Total Water Content, Partition Between Extracellular Compartment and Cells, Concentration of Electrolytes, and Capacity to Retain or Excrete Administered Water and/or Electrolytes: (*a*) Selection of appropriate corrective solution depends upon the nature of the fluid lost and is made in accordance with Table 6. Hemorrhage is obviously combated most effectively by blood transfusion. The circulatory collapse associated with extravasation of plasma into injured tissues can also be overcome by blood transfusion; however, the associated hemoconcentration may be corrected by plasma # or substitutes. If dehydration resulted from the loss of body fluids which were, in toto, approximately neutral, the plasma pH and relative chloride and bicarbonate concentration of the patient's blood will remain approximately normal, and lactated Ringer's solution will be adequate for replacement of the water and sodium deficit.

Metabolic acidosis is suspected when relatively more alkali was lost (as in diarrhea) or when relatively more acid was ingested or produced (as in ketosis); its presence is confirmed by low pH and relatively low bicarbonate concentration; its correction requires an increased proportion of alkali in the therapeutic solutions. Metabolic alkalosis is suspected when relatively more acid was lost (as in vomiting) or when considerable alkali was administered; its presence is confirmed by elevation of blood pH and bicarbonate concentration. The body attempts to adjust to metabolic alkalosis by cellular uptake of sodium; this displaces potassium, the subsequent excretion of which leads to somatic depletion. Sufficient potassium chloride to correct the deficit is given slowly, according to the precautions given below, the employment

TABLE 6.—*Isotonic Solutions Given to Correct Hypotonic Dehydration*

Patient's Status in Addition to Deficit of H_2O and Na	Fluid Used for Correction	Composition, mEq./100 Ml.					Volume for Correction
		Na	K	Cl	Lact.	HPO_4	
Hemorrhage	Blood	8	0.2	6	2	0.1	Depends upon estimated needs based on measured or estimated losses prior to the initial examination and the clinical condition at that time
Extravasation of plasma	Plasma	14	0.4	10	3	0.2	
Acid-base balance compensated	Lact. Ringer's	14	0.4	11	3.4	...	
Metabolic acidosis	1/6 M Na lactate*	16	...	..	16	...	
Metabolic alkalosis	Isotonic NaCl†	15	...	15	...	...	
Hypokaliemia	Isotonic KCl,‡ 1.15%	..	15	15	...	...	
Hypophosphatemia	Buffered Na phosphate§	14	...	..	...	14	

* Lactate is converted into HCO_3 by the normal liver in one to two hours; when liver is damaged, use 1/7 M sodium bicarbonate in place of lactate.

† Metabolic alkalosis is usually accompanied by potassium depletion and will require the administration of potassium chloride as well as sodium chloride. For every liter of repair solution, from 100 to 300 ml. isotonic KCl should be mixed with from 700 to 900 ml. isotonic sodium chloride solution.

‡ Potassium chloride is never given parenterally in concentrations exceeding 45 mEq. per liter; therefore, from 100 to 300 ml. of isotonic KCl should be added to 700 to 900 ml. of an appropriate isotonic sodium-containing solution to make a total of 1 liter for administration.

§ Composition 24.66 gm. Na_2HPO_4 and 2.24 gm. NaH_2PO_4 per liter.

¶ However, in water intoxication the final sum total solution is hypertonic, as the result of large excess of sodium required for corrective measure, given in a minimal volume of water.

Plasma should not be used unless contamination by the homologous hepatitis virus has been minimized.

of this salt also aiding in restoration of the depleted chloride. Provided potassium chloride is utilized to restore the potassium depletion of metabolic alkalosis, the chloride deficit can be adequately corrected by the concomitant use of "physiologic" saline. Isotonic saline solutions contain chloride in concentrations significantly higher than in the extracellular compartment (surplus of approximately 4 mEq. per 100 ml.); after infusion into chloride-depleted patients, the tendency to retention of the chloride and excretion of part of the sodium accentuates this discrepancy and thereby corrects the underlying condition. Ammonium chloride is not advisable in metabolic alkalosis because of the toxicity of ammonia and the accentuation of the potassium deficit.

Potassium deficits are usually present not only in metabolic alkalosis but also in hypotonic dehydration with normal or lowered plasma pH and commonly must be corrected to achieve full recovery. Hypophosphatemia usually develops during recovery from diabetic coma, and buffered phosphate solution (Table 6) is employed to correct the deficit, if the patient is unable to take oral feedings.

(*b*) Estimation of the volume of the selected corrective solution is based upon the severity of the hypotonic dehydration in the individual patient. Unless the dehydration is very severe, the volume used for corrective purposes during the first day should not exceed 3 liters. The total volume to be given during the first 24 hours also includes, in addition, the estimated fluids for replenishment of losses anticipated during this period. If clinical and laboratory examinations after the first 24 hours reveal that hypotonic dehydration is still present, the objective is reached by the administration of further corrective solutions in addition to those needed for current replenishment.

(*c*) Estimation of electrolyte composition of the corrective solution is made from the presumed composition of the losses. The electrolyte composition of extravasated blood and plasma need not enter into the calculations as long as transfusions are used for restoration. When the dehydration resulted from the loss of body fluids, the electrolyte composition of the corrective solution is adjusted in accordance with the nature of the losses. Although hypotonic dehydration is characterized by depletion of both water and sodium, the term implies a relatively greater deficit of the latter. Repair solutions of isotonic sodium concentration are effective in correction of hypotonic dehydration because the body eliminates relatively more of the administered water than sodium.

Metabolic acidosis is corrected by the administration of part of the total estimated corrective solutions in form of ⅙ M sodium lactate.* Although the proportion given as sodium lactate depends upon the severity of the acidosis, the usual needs are fulfilled by 0.5 to 2 liters of ⅙ molar sodium lactate.† The remainder of the volume for correction of metabolic acidosis is composed of lactated Ringer's solution. The sodium, chloride, and water deficits of metabolic alkalosis are corrected by isotonic sodium chloride solution in amounts up to 3 liters daily. The utilization of potassium will be discussed in the section on the treatment of hypokaliemia.

2. Provision of Water and Electrolyte During the Next Twenty-Four Hours to Replenish Losses Predicted During That Period: This prediction is based upon the measured or estimated losses during the preceding 24 hours.

(*a*) The volume of extravasated blood, urine, stools, vomitus, and exudate should be measured whenever possible. The measured or estimated blood loss represents the amount required for replacement. The sum total

* Lactate is converted into bicarbonate by the normal liver in one to two hours; sodium bicarbonate in ⅙ molar solution should be substituted for isotonic sodium lactate in the presence of liver damage, anoxia, and beriberi, since lactate catabolism is impaired.

† Overcorrection with sodium lactate or bicarbonate is not advisable, since continued hyperventilation will then produce alkalosis. An untoward effect of this type may be encountered, particularly in the treatment of diabetic acidosis with sodium lactate or bicarbonate.

volume of urine, stools, vomitus, and exudate escaping by drainage or suction represents the volume required to replace losses through these avenues. To the foregoing figures, one must add the estimated volume of sweat and insensible perspiration (Table 7) to obtain the total volume lost during the preceding 24 hours and thus the amount predicted for replacement. The insensible water loss may be estimated from insensible loss of weight determined daily by accurately weighing the patient, all ingesta, and all excreta. Even though standard scales only are available, weighings made as accurately as possible

TABLE 7.—*Estimation of Loss During Preceding Twenty-Four Hours*

Body Fluid Lost	Volume	Composition, mEq./100 Ml. Determined by Analysis, if Possible; Otherwise Estimated				
		Na	K	Cl	HCO_3	HPO_4
Blood plasma (estimated 55% of total blood loss)	Measure if possible;	14	0.4	10	3	0.2
Urine 1.5 to 2.5 L./day	estimate if no	7 (0.5-14)	4 (0.5-10)	5 (0.5-10)	0 (0.3)	5 (0.2-10)
Vomitus	measurement	7 (2.5-10)	1.5 (1.0-2.5)	14	0	0.2
Diarrhea		14	0.7 (0.5-1.0)	9 (3-10)	5 (3-10)	..
Sweat	Estimated	3 (0.5-10)	1 (0.5-3.0)	3 (0.5-10)	..	..
Insensible perspiration estimated at 40% above basal	17 ml./kg./day	..	..	..	..	..

TABLE 8.—*Hypothetical Seventy Kilogram Patient with History of Diarrhea for Two Days and Admitted in Hypotonic Dehydration with Metabolic Acidosis*

	Volume, Ml.	Na, mEq.	K, mEq.	Cl, mEq.	HCO_3, mEq.
A. Estimated requirements for correction of initial status and replenishment during the first 24-hour period					
1. Correction of abnormalities					
Water and electrolytes believed needed to restore normal hydration	2000	280	15	160	120
2. Replenishment					
Water and electrolyte believed needed to replenish loss predicted for the next 24-hour period					
Urine	500	15	20	25	0
Vomitus	0	0	0	0	0
Diarrhea	1500	210	11	120	90
Sweat	0	0	0	0	0
Insensible loss	1200	...	..	...	...
Total	5200	505	46	305	210
B. Preparation of prescription to fulfill sum total requirements for correction and replenishment					
1. Use of concentrated or molar stock solutions of electrolyte					
Molar sodium lactate	150	150	..	...	150
Concentrated lactated Ringer's	100	370	10	270	68
Concentrated potassium chloride ampule	40	...	40	40	...
5% dextrose in water	5000	...	..	...	...
Total*	5280	520	50	310	218
2. Use of isotonic stock solutions of electrolyte					
1/6 molar sodium lactate	900	144	..	...	144
Lactated Ringer's solution, containing 5% dextrose	2500	350	10	275	85
1.15% KCl	250	...	37	37	...
10% dextrose in water	1500	...	..	...	...
Total†	5250	494	47	312	229

* The total for the 24 hours is divided into five infusions, each comprising 1000 ml. 5% dextrose, 30 ml. molar sodium lactate, and 20 ml. concentrated lactated Ringer's solution. Five milliliters of concentrated potassium chloride solution is added to four of the five infusates.

† The isotonic KCl (1.15%) is added to the dextrose infusate, so as to dilute the potassium. The total 24-hour volume of sodium lactate, lactated Ringer's, and 10% dextrose, containing potassium chloride, is divided among 5 infusions, distributed throughout the 24-hour period.

serve to detect gross changes and to thus check predictions. For obvious reasons, such measurements may be impractical for severely ill patients. For the average adult, the insensible loss may be estimated at 40% above the basal, or 17 ml. per kilogram per day. In the presence of hyperthyroidism, fever, undue activity, etc., this estimate must be revised upwards.

(*b*) The electrolyte content of extravasated blood is usually not included in the calculations, since transfusions must be used for replacement if blood loss is of any significance. The electrolyte composition of exudates is comparable to that of plasma. Quantitative analysis of sodium, potassium, and chloride lost in the 24-hour urine, stools, vomitus, and gastrointestinal suction is desirable. Such data provide a much more precise basis for electrolyte replenishments. In the absence of analyses, estimates must be substituted, utilizing the average composition given in Table 7 unless examination of the patient has revealed factors, such as renal or adrenal disease, that would suggest an electrolyte excretion at one of the extremes indicated in the Table.

Until the kidneys are able to compensate for errors in water and electrolyte intake, a state of normal hydration is maintained by adjustment of water and electrolyte intake to correspond with predicted losses. The water requirement is equivalent to the total measured or estimated volume lost during the preceding 24 hours. If the plasma concentration of a given electrolyte is normal, its intake should correspond with the total amount lost during the preceding 24 hours; if the plasma concentration is abnormal, appropriate adjustments are necessary.

Each morning the tentative prescription for the next 24 hours is made from the volume and estimated electrolyte content of the fluid lost from each channel. If chemical analyses performed during the day deviate widely from those anticipated when the prescription was formulated, appropriate modification is made in the afternoon. In the prescription, consideration must be given not only to volume and electrolytes but also to caloric content, since failure to provide sufficient calories to minimize protein catabolism will release cellular electrolyte and thus alter the composition of the extracellular compartment. If the projected intake is between 1000 and 2000 ml., it should contain 20% to 15% glucose to meet carbohydrate needs; if it exceeds 2000 ml., 15% to 10% glucose may be sufficient.

The method of preparation of a fluid and electrolyte prescription is best illustrated by a hypothetical case of hypotonic dehydration with metabolic acidosis. This prescription must provide for (*a*) correction of the present status in respect to water content and electrolyte composition and (*b*) replenishment of losses predicted during the next 24 hours. The initial deficits are estimated from history of losses and the initial history and physical examination; these are expressed in Table 8 in terms of water volume and milliequivalents of each electrolyte and serve as a basis of the requirements for correction. The estimated water and electrolyte content of the losses during the preceding 24 hours is entered on the same table and serves as a basis for the replenishments predicted during the next 24 hours. Simple addition of the volumes and electrolyte content of the corrective and replenishment solutions gives a sum total for the next 24 hours.

When the prescription is prepared for the next 24 hours, the electrolyte requirements are first fulfilled by the use of concentrated or molar solutions of lactated Ringer's, sodium chloride, sodium lactate, or sodium

TABLE 9.—*Composition of Concentrated and Molar Electrolyte Solutions*

	mEq. per 10 Ml.			
	Na	K	Cl	HCO_3
1. Conc. lactated Ringer's (25 times isotonic)	34	1	28	8.4
2. Molar NaCl (approx. 6%)	10	0	10	0
3. Molar Na lactate	10	0	0	10
4. Conc. $NaHCO_3$ (3.75 gm./50 ml.)	8.9	0	0	8.9
5. Conc. KCl (20 mEq./10 ml.)	0	20	20	0

bicarbonate solution or a combination, depending upon the individual circumstances. The composition of concentrated or stock solutions in milliequivalents per 10 ml. is given in Table 9 and serves as a reference for each individual case. The volume of each concentrated electrolyte solution is added to an appropriate amount of glucose in water isotonic solutions in milliequivalents per 100 ml. is given in Table 6 and is used to determine the amounts of each electrolyte needed for the individual patient. To the estimated volume of electrolyte is added the appropriate volume and concentration of glucose in water to make up the total 24-hour prescription.

TABLE 10.—*Same Patient as in Table 8*

If the diarrhea is improved, but not checked, during the day and the examination at the end of 24 hours still shows dehydration and the following plasma levels, Na 130, K 3.0, Cl 88, HCO_3 17 mEq./L., further correction is necessary therapeutically

	Volume, Ml.	Na, mEq.	K, mEq.	Cl, mEq.	HCO_3, mEq.
A. Estimated requirements for correction of status at the end of 24 hours and replenishment during the next period					
1. Correction of abnormalities					
Water and electrolytes believed needed to restore normal hydration and chemical balance (i. e., sufficient sodium to restore hydration and to raise level by 5 mEq. per liter and amounts of bicarbonate and potassium believed necessary)..	1000	340	67	240	160
2. Replenishment					
Predicted losses during the 24 hr. period					
Urine	1000	10	40	50	0
Vomitus	0	0	0	0	0
Diarrhea	750	105	5	60	45
Sweat	0	0	0	0	0
Insensible loss	1200	0	0	0	0
Total required	3950	455	112	350	245
B. Preparation of prescription to fulfill sum total requirements for correction and replenishment					
1. Use of concentrated or molar stock solutions of electrolyte					
Molar sodium lactate	150	150	0	0	150
Concentrated lactated Ringer's*	80	296	8	216	68
Concentrated potassium chloride ampules (20 mEq./10 ml.)	50	0	100	100	0
10% dextrose in water	3600	...	..	...	...
Total	3880	446	108	316	248
2. Use of isotonic stock solutions of electrolyte					
1/6 molar sodium lactate	1000	160	..	...	160
Isotonic lactated Ringer's containing 5% dextrose	2000	280	8	220	68
1.15% KCl	600	...	90	90	...
10% dextrose in water	1000	...	..	...	...
Total	4060	440	98	310	228

* The concentrated electrolyte solutions are diluted in the dextrose solution.

to make up the sum total volume for the next 24 hours. The concentration of the glucose will depend upon the total volume and, in general, is in the 20% to 15% range for volumes of 1000 to 2000 ml., 15% to 10% for volumes of 2000 to 3000 ml., and 10% to 3% for volumes more than 3000 ml.

As an alternative, the electrolyte requirements may be fulfilled, partly or wholly, by isotonic stock solutions instead of concentrated or molar solutions. The composition of

B. Asymptomatic Hyponatremia.—Treatment should be directed at the disease causing the malnutrition and hyponatremia. Attempts to correct the hyponatremia per se are of no avail and may lead to edema.

C. Water Intoxication.—1. Selection of an Appropriate Corrective Solution: Administration of a hypertonic sodium solution in divided doses is essential in patients with acute cerebral manifestations of water intoxication and in certain cardiac patients with the

"low salt syndrome." Concentrated lactated Ringer's solution is suitable when there is no significant abnormality in plasma pH; concentrated sodium chloride is advisable when there is associated alkalosis; a hypertonic mixture of sodium chloride and lactate is substituted when water intoxication is complicated by acidosis. The proportion of sodium lactate is adjusted in accordance with the degree of acidosis. If impaired hepatic

tion in sodium concentration. Since volumetric determinations may be neither available nor possible, the approximate needs for sodium may be estimated from the plasma level. The plasma sodium concentration will be raised approximately 1 mEq. per liter by a dose of hypertonic sodium solution, supplying 0.6 mEq. per kilogram body weight. In the initial estimate for the treatment of water intoxication, one should not attempt to

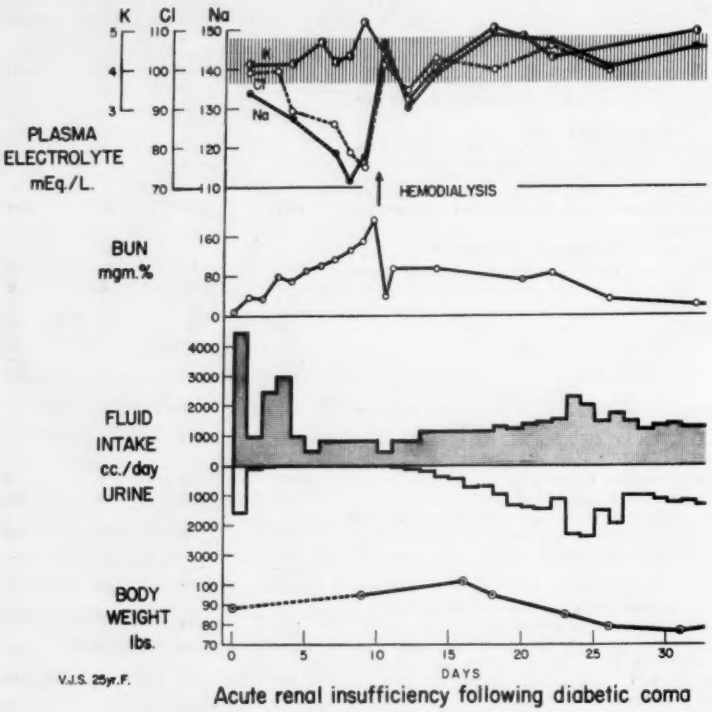


Fig. 23.—V. J. S., a 25-year-old woman, was admitted in diabetic coma with dehydration, shock, and pyelonephritis. During the patient's recovery from diabetic coma, anuria developed, as a result of acute renal failure ("lower nephron nephrosis"). The excess water administered on the third and fourth days produced hyponatremia and typical clinical manifestations of water intoxication. With sharp restriction of fluids, the patient improved temporarily, but the plasma sodium levels fell progressively and the patient again became semiconscious. On the 10th day, hemodialysis was performed with the artificial kidney. This resulted in marked reduction in blood urea nitrogen, correction of hyponatremia and hypochloremia, and return to consciousness. With onset of significant diuresis, on the 16th day, gradual improvement of uremia took place.

catabolism of lactate is anticipated, sodium bicarbonate should be employed instead.

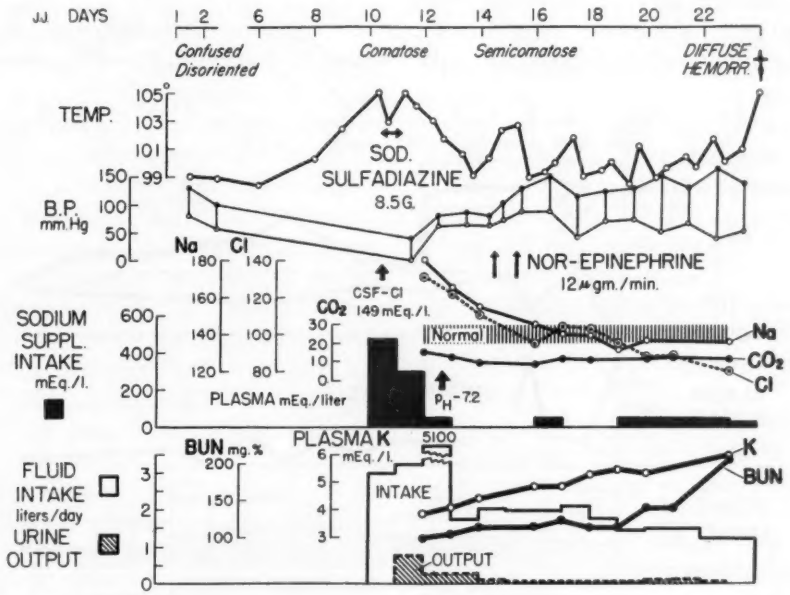
2. Volume and Concentration of Corrective Solution: The sodium deficit may be calculated in milliequivalents by multiplying the volume of total body fluid by the reduc-

raise the plasma sodium concentration by more than 5 to 10 mEq. per liter.

The tonicity of the corrective solution depends upon the condition of the patient and the facilities for administration. Hypertonic solutions must be given into the vein, because

of the irritation caused by extravascular injection. They attract water from the tissues into the blood stream to abruptly raise blood volume and should be injected slowly over a period of 20 to 30 minutes, particularly in patients with heart disease. Molar solutions represent maximal concentrations ordinarily tolerated intravenously in the absence of cardiac insufficiency. Since molar solutions of sodium salts contain 1 mEq. per ml., the amount estimated to raise the extracellular sodium level by 10 mEq. per liter is obtained by multiplying the weight in kilograms by 6 ml. molar solution. When there is danger of precipitation of pulmonary edema by a molar solution, a half molar strength may be substituted at a still slower rate and the initial efforts at correction should be estimated to raise the plasma sodium level by no more than 5 mEq. per liter. Regardless of whether a molar or half molar solution is selected, it should be given in divided doses. Each individual injection should not exceed 100 ml. and should be given over a 20- to 30-minute period; it is repeated after rest periods of ½ to 1 hour until the manifestations of water intoxication have been relieved.

3. Other Sources of Fluid Intake: In dehydration, the initial estimate provides for



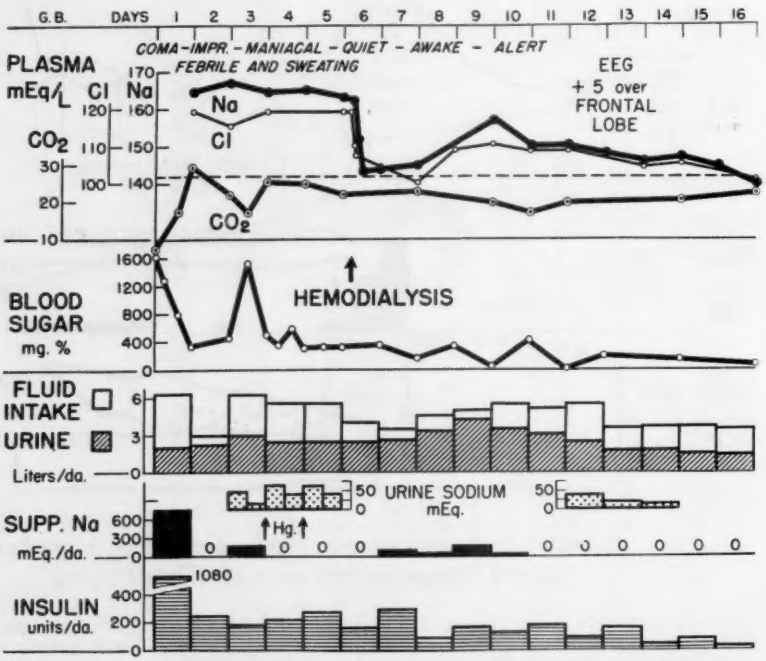
Development of hypernatremia and hyperchloremia in psychotic patient followed by fatal acute renal insufficiency

Fig. 24.—J. J., a 25-year-old woman, was admitted with schizophrenia, as a consequence of which she refused all oral feedings. After eight days of parenteral infusions of isotonic sodium chloride solution, hyperthermia and coma developed. As a result of an erroneous diagnosis of pneumonia, 8.5 gm. sodium sulfadiazine was given, but cerebral manifestations were believed to be unrelated to the therapy. A lumbar puncture, performed because of coma, revealed cerebrospinal fluid chloride to be 149 mEq. per liter. Between the performance of the lumbar puncture and the report of the results, an additional 5 liters of "physiological" saline were given. When she was referred to the medical department, the patient was in coma, with hypertonic dehydration, circulatory collapse, and anuria and there were the following abnormalities in plasma: Na, 180 mEq. per liter; Cl, 135 mEq. per liter; pH, 7.2. The intravenous infusion of 5% dextrose in water with arterenol corrected dehydration and circulatory collapse and restored plasma sodium levels to normal; however, coma or semicoma and anuria persisted, resulting in death. Autopsy showed diffuse petechial hemorrhages, which, along with the clinical and chemical findings, were attributed to the hyperosmolarity syndrome.

correction of the abnormality and for replenishment of the losses anticipated in the next 24 hours. In water intoxication, the employment of hypertonic sodium solutions, as described above, provides for correction. In estimating the requirements for replenishment during the next 24 hours, fluid intake must be reduced to a minimum until the patient has recovered from water intoxication. Overhydrated patients are improved by maintenance of a negative water balance. This is established by the use of a hypertonic solution of a sodium salt for corrective purposes and is maintained by the use of a hypertonic solution of glucose as a source of calories. In the milder cases of water intoxication, recovery may occur merely from maintenance of a negative water balance, without the injection of concentrated solutions of electrolyte. The volume of the repair solution is kept very low and the calorie content high by the use of hypertonic glucose solutions.

4. Promotion of the Excretion of Water and Retention of Sodium: Hydrocortisone causes retention of sodium and also facilitates rejection of excess water. It is obligatory in the treatment of water intoxication associated with Addison's disease and may be desirable under other circumstances. Digitalization is of value in the elimination of water retained in cardiac decompensation. In selected cases, prompt adjustment of electrolyte concentrations may be achieved with the artificial kidney (Fig. 23).

D. Hypertonic Dehydration and Hyperosmolar Syndrome.—1. Promotion of water in-



Hyperosmolarity syndrome complicating diabetic coma

Fig. 25.—J. G., a 32-year-old man, was admitted in diabetic coma and dehydration with severe hyperglycemia and acidosis. During the first 24 hours, the patient received 1080 units of regular insulin and 6020 ml. of fluids, containing 750 mEq. of sodium. Although the initial response to treatment was favorable, the patient became irrational and maniacal, owing to hyperosmolarity syndrome. This persisted despite a high fluid and no sodium intake, probably because of excessive fluid loss through skin and lung and excretion of urine with low sodium concentration, aggravated by dysfunction of the frontal lobe, as suggested by a subsequent electroencephalogram. The patient was dialyzed with the artificial kidney, with prompt correction of the chemical abnormalities and improvement of mental status.

take in sufficient amounts to replace deficit and restore plasma sodium concentration to normal is accomplished by deliberate administration of adequate amounts of tap water by mouth or rectal drip or by the administration of an adequate volume of 5% dextrose in water parenterally. A positive water balance and a gain in weight should be obtained.

2. Sodium Intake Must Be Stopped: The precipitation of the hyperosmolar syndrome by the use of isotonic saline and its aggravation by failure to immediately stop sodium intake are exemplified by Figure 24. Sodium excretion may be promoted by the use of the mercurial diuretics in nondehydrated patients with the hyperosmolar syndrome. Prompt adjustment of the electrolyte concentration may be achieved with the artificial kidney (Fig. 25). Hypokaliemia is a common complication and should be investigated after recovery from circulatory collapse and oliguria. The deficit is corrected by supplementary potassium, as discussed below.

E. Asymptomatic Hypernatremia.—Therapy for this condition resolves itself into the treatment of the cause. Reduction of sodium intake and increase of water are alone insufficient for permanent effects.

F. Edema.—Treatment has been well covered elsewhere and therefore is omitted from this discussion.

G. Hyperkaliemia.—1. Eradication of the cause: This is an objective that is seldom attainable. When insufficiency of mineralocorticoids or glycocorticoids is responsible or when it is a contributing factor, the treatment is patterned after that for adrenal insufficiency. When hyperkaliemia is traceable to extrarenal factors that have critically reduced renal plasma flow and glomerular filtration rate, the treatment is directed towards these extrarenal factors and includes restoration of blood volume and the combatting of cardiac insufficiency and peripheral circulatory collapse. When urinary tract obstruction is responsible for the anuria and hyperkaliemia, the specific treatment is urological.

2. Prevention of Ingress of Potassium into the Extracellular Compartment: This is essential. The exogenous intake of potassium should be reduced to zero. Transfer of cellular potassium to the interstitial space should be prevented, insofar as possible, by (*a*) the administration of adequate glucose and fat to minimize endogenous protein catabolism, (*b*) surgical removal of devitalized tissue that may be a source of potassium absorption, and (*c*) specific treatment of diseases associated with release of potassium from the cells to plasma (Table 4).

3. Promotion of Potassium Transfer from Interstitial Tissue to Cells: This may reduce plasma potassium concentration. One of the purposes of the high-carbohydrate intake is the promotion of glycogenesis and the consequent deposition of potassium in the cells. Supplementary insulin in doses that do not produce hypoglycemia may be of aid. Concomitant stimulation of protein anabolism may also store potassium but probably cannot be accomplished as long as the intake of protein and amino acids is prohibited. Testosterone propionate may be employed in doses of 25 mg. daily intramuscularly for five days, but an agent with greater protein-anabolic and less androgenic activity is needed.

4. Promotion of Potassium Excretion Through Other Channels: This is usually necessary. Since salivary, gastric, and intestinal secretions contain potassium in concentrations from 1.5 to 4 times that in the plasma, their removal by gastric or intestinal suction tends to check further rise in plasma potassium level and may cause a significant reduction. Enemas containing ion-exchange resins in suspension increase fecal elimination of potassium at the expense of exchange with another cation. The absorption of the cation released by this exchange may be harmful, particularly when ammonium resins are employed. Sodium resins will be helpful when there is associated hyponatremia. The most effective method of extrarenal elimination of potassium is by the use of the artificial kidney. The plasma concentration may be

reduced significantly within two hours, but hemodialysis is usually continued for four to six hours in order to remove sufficient potassium. As much as 120 mEq. of potassium may be removed by this procedure.

5. Regulation of Intake of Water and Electrolytes Other Than Potassium: This depends upon the initial clinical status and the losses anticipated in the next 24 hours. If the patient is normally hydrated, the volume administered during the next 24 hours should not significantly exceed the losses; otherwise, water retention will occur. Dilution of extracellular fluid is a common sequel and occurs when there is relatively more retention of water than of sodium. The regulation of intake to replenish current losses has been discussed. Hyponatremia aggravates the clinical manifestations of hyperkaliemia and should be corrected. Calcium gluconate, intravenously, is of some symptomatic benefit in hyperkaliemia.

H. Hypokaliemia. — Hypokaliemia usually reflects a primary deficit in tissue potassium unless it is produced by (1) a marked expansion of extracellular volume from injection of potassium-free fluids or (2) excessive uptake by cells avid for potassium, as in anabolic states and periodic family paralysis (Table 4). Thus, the potassium must be administered in quantities sufficient to correct intracellular as well as extracellular deficits. As long as urinary volume is normal, potassium given at a physiologic rate is nontoxic. A surplus should, therefore, be given to correct losses, since extra potassium will be promptly eliminated. The quantity and route of administration depend upon the severity of the deficit and nature of the illness.

1. Correction by the Oral Route: This is the method of choice when food can be eaten and retained; a normal mixed diet, supplying approximately 100 mEq. potassium daily (usual range, 80 to 120 mEq.), will eventually suffice. If oral feedings are restricted, but not prohibited, one may make use of simple foods, such as orange juice, milk, and bread, each of which furnishes 3.5 to 4.5 mEq. potassium per 100 gm. Furthermore, the use of food to refurbish depleted potassium stores is preferable because it also supplies other materials utilized anabolically, particularly protein and carbohydrate. Since repletion of potassium from diet alone may require many days, supplements may be given to bring the potassium intake up to a maximum of 3 mEq. per kilogram (120 to 200 mEq. per day), depending upon the magnitude of the losses and degree of hypokaliemia. Enteric-coated potassium chloride in doses of 1 gm. three times a day furnishes 40 mEq. potassium; it is well tolerated by most persons in doses up to 3 to 4 gm. three times a day, but may cause gastrointestinal irritation, and great caution sometimes must be exercised in the administration of potassium salts to anyone whose urinary volume is below 500 ml. per 24 hours. In the event of severe oliguria and/or adrenal insufficiency, pronounced downward revision of the dosage and control by either blood potassium determinations or electrocardiogram is obligatory.

2. Correction by the Parenteral Route: The parenteral route is employed in critical cases or when potassium cannot be taken or retained orally. The alkalosis produced by incessant vomiting is invariably accompanied by potassium depletion and will usually require potassium by the parenteral route. Potassium chloride is the advisable salt and is stocked either as a sterile isotonic (1.15%) solution or as commercial ampules that are even more concentrated. Potassium chloride should not be administered in a concentration exceeding 45 mEq. per liter or at a rate greater than 20 mEq. per hour. Thus, if the stock solution is isotonic KCl, containing 15 mEq. potassium per 100 ml., from 100 to 300 ml. should be mixed with 900 to 700 ml. of the appropriate corrective solution to make a liter for slow parenteral infusion. This will supply from 15 to 45 mEq. potassium. The total amount given per 24 hours will depend upon the total requirements minus the portion supplied by the oral route.

I. Hypomagnesemia. — Patients able to partake of food rarely require supplementary

magnesium. For parenteral therapy, 1 to 2 gm. of magnesium sulfate (50% solution), given intramuscularly four times a day, should be adequate in most cases, or 100 ml. of a 2% solution may be given intravenously for immediate effects.

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Effects of Parenterally Administered Reserpine

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Reserpine is being widely used for the control of hypertension * and as a tranquilizing agent.[4] Its use in the management of the acutely disturbed patient is limited by the delayed action following oral administration. In an effort to obtain more rapid onset of action, large doses of reserpine were administered parenterally to nine acutely disturbed subjects. This method of administration has been discontinued because of complications and lack of therapeutic response. Our observations are presented in this report.

REPORT OF CASES

CASE 1.—A 50-year-old white male chronic alcoholic was admitted to the hospital with tremors and hallucinations which developed after heavy drinking of 10 days' duration. One year previously he had been treated for delirium tremens. Physical examination revealed a blood pressure of 130/90 mm. Hg; pulse rate, 100; respirations, 25, and temperature, 99 F. There were no abnormal physical findings. Reserpine, 15 mg., was administered intravenously. The blood pressure immediately thereafter was unaltered, and there were no changes in his general condition during the next several hours. The following day the tremors and hallucinations subsided, but the patient complained of headache and dizziness. While the patient was recumbent the blood pressure was 110/70, but it dropped to 80/60 when he was upright. Bed rest was ordered, and the next morning the headache and dizziness subsided and the blood pressure had stabilized at normal values.

This case is an example of orthostatic hypotension noted about 12 hours after the intravenous administration of 15 mg. of reserpine.

CASE 2.—A woman approximately 60 years of age was severely agitated. A history of drug or alcohol ingestion could not be obtained. On admission, the blood pressure was 130/80 mm. Hg; pulse, 86; respirations, 20, and the temperature, 98.6 F. There were no abnormal physical findings. Reserpine, 15 mg., was given intravenously over a three-minute period. Within the next one and one-half hours, there was a slight drop in blood pressure, to 120/70, and the patient began to have profuse diarrhea. Four hours after drug administration, the blood pressure was unobtainable and the skin was cool and moist. The patient was placed in the shock position; oxygen was administered, and 5% dextrose in saline with arterenol (Nor-epinephrine), 0.4 mg., was given intravenously. Bradycardia (rate, 55 per minute) was noted. The blood pressure rose to 40/0 about 30 minutes after the infusion was started but thereafter was unobtainable. The patient died six hours after receiving reserpine and two hours after the onset of shock. The electrocardiogram (Fig.), taken shortly after the infusion was begun, was interpreted as follows: Sinus rhythm, rate 56, provided the pause after the ectopic beats is compensatory. It is possible but less likely that the sinus rate is 28. Each beat of sinus origin is followed by one or, sometimes, two ectopic beats from multiple foci. The T-waves of the beats of sinus origin are greatly increased in amplitude and greatly widened, and Q-T of these beats is greatly prolonged—more than 0.68 second. Exact measurement of Q-T interval is not possible, because the ectopic beat starts before the T of the beat of sinus origin is completed. P, P-R, and QRS of the beats of sinus origin are normal. In view of the history, these changes are consistent with a direct toxic effect on the myocardium.†

This case illustrates the development of shock and death following intravenous administration of 15 mg. of reserpine to an extremely agitated patient with an acute psychosis.

CASE 3.—A 60-year-old man with marked tremulousness from acute alcoholism was given 5 mg. of reserpine intravenously. Blood pressure prior

From the District of Columbia General Hospital.

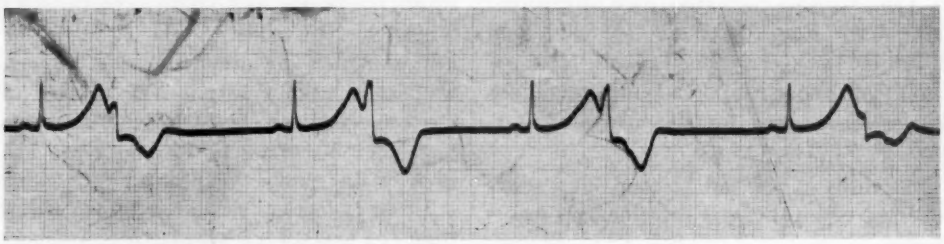
Reserpine was supplied by Ciba Pharmaceutical Products, Inc., Summit, N. J.

* References 1-3.

† Interpretation of the electrocardiogram by Dr. Albert D. Kistin.

to drug administration was 130/80 mm. Hg. One hour later he was sitting up in bed complaining of difficulty in breathing. Examination disclosed a generalized flushing of the skin and a few fine inspiratory rales posteriorly. The blood pressure at this time was 100/60 mm. Hg; pulse rate, 80, and respirations, 22. In the next hour the flushing partially subsided, but the blood pressure fell to 80/55 with no change in pulse or respirations. The patient was placed in the shock position and given intravenously a solution of 1000 cc. of 5% dextrose in saline and 4 mg. of arterenol. The blood pressure was regulated at 110/60 mm. Hg by this infusion, and four hours later shock therapy was discontinued. The patient maintained his normal blood pressure thereafter, and the flushing of the skin completely disappeared.

CASES 4-9.—Four subjects with psychomotor agitation resulting from acute alcoholism were given reserpine intravenously to allay their apprehension and diminish motor excitability. A single dose was given, and the amounts employed were 4, 5, 10, and 15 mg. Two additional patients with acute alcoholism were given 5 mg. of reserpine intramuscularly every 8 hours over a 24-hour period. There were no complications in this group of subjects; however, despite the large doses employed, neither tranquilization nor sedation was achieved and other medication was subsequently required.



Electrocardiogram (Lead II) of patient reported in Case 2.

SUMMARY

Reserpine was administered parenterally in doses from 4 to 15 mg. to nine acutely disturbed subjects. Orthostatic hypotension was noted in two subjects, and another died in shock. The electrocardiogram in the latter case revealed changes suggestive of myocardial toxicity, a finding that may account in part for the irreversible hypotension. Diarrhea has been observed following intravenous reserpine in dogs [5] but not in other animals. The loss of fluid and electrolytes attendant with diarrhea may have also contributed to the development of the shock syndrome.

The generalized flushing of the skin and respiratory distress noted in one of the subjects with orthostatic hypotension raises the possibility of an allergic reaction to the drug.

The parenteral administration of reserpine in the management of acutely disturbed alcoholics does not seem warranted in view of the lack of therapeutic response and occasional severe complications.

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Sickle Cell Trait and Disease in Pulmonary Tuberculosis

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The relatively high frequency of tuberculosis in the Negro has for a long time been a subject for speculation. Low racial resistance and poor socioeconomic conditions have been blamed for this increased incidence.[1]

Recently, Weiss and Stecher [2] in a series of 150 Negro patients with pulmonary tuberculosis found that 12.6% had sickle cell trait, whereas in another group of 150 Negroes without pulmonary tuberculosis only 5.3% had the sickling trait. Moreover, of the 19 who had both sickle cell trait and pulmonary tuberculosis, 14, or 74%, had exudative lesions, whereas only 38% of those with pulmonary tuberculosis but without sickle cell trait had exudative lesions. This led these observers to hypothesize that the sickle cell trait might not only contribute to the increased incidence of pulmonary tuberculosis in the Negro but might also influence the extent of the disease present. In contrast to the figures of Weiss and Stecher is a smaller series of 77 tuberculous Negroes at Sea View Hospital, Staten Island, N. Y.,[3] in which the incidence of sickle trait was 5.2%.

The incidence of sickle cell trait in the American Negro population varies in different regions, ranging in general from 6% to 10%. The average figure from the Borough of Brooklyn is 8%.* Neel [4] has shown that sickle cell trait is the expression of heterozygosity of the sickle cell gene, while sickle cell anemia is the expression of homozygosity. Pauling and co-workers [5] showed that the hemoglobin (S) of sickle cells has a different electrophoretic mobility from normal (A) hemoglobin. In sickle cell anemia all of the hemoglobin is abnormal in this respect, whereas in sickle cell trait 27% to 44% of the hemoglobin is hemoglobin S and the remainder is normal or fetal in type. The ratio of the number of persons with sickle cell trait to cases of sickle cell anemia varies from 7 : 1 to 40 : 1, with the latter figure more generally agreed upon.

It was our purpose to attempt to study the relationship, if any, between pulmonary tuberculosis and the sickle cell trait.

METHODS

1. Two hundred consecutive American-born and West Indian Negroes who were proved to have pulmonary tuberculosis and were either inpatients or clinic patients of the thoracic disease services of the Kings County Hospital were included. No patients of Puerto Rican extraction were included, because of difficulty in racial classification.

2. All patients were classified as to age, sex, and classification of the maximum extent of the pulmonary tuberculosis present, according to the standards of the National Tuberculosis Association.[6]

3. The blood of each patient was studied by making two sickle cell preparations, using freshly prepared 2% sodium metabisulfite as the reducing agent. Each preparation was examined microscopically with low and high power at 15 minutes and 1 hour.

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* Watson, R. J.: Personal communication to the authors.

4. All patients found to have a positive sickling preparation were further evaluated to determine if they had the sickle cell trait or sickle cell anemia. This was done by (*a*) history, (*b*) physical examination, (*c*) blood studies, (*d*) filter paper electrophoresis, and (*e*) x-ray survey, including the skull, dorsolumbar vertebra, and hands and feet, including fingers and toes.

RESULTS

Of the 200 Negroes with pulmonary tuberculosis 16 were found to have preparations positive for sickling, an incidence of 8%. Of these 16, fifteen were proved to have the sickle cell trait, an incidence of 7.5%. One patient had both far-advanced pulmonary tuberculosis and sickle cell anemia, proved by history, physical examination, x-ray studies, and electrophoresis. The break-down of our 200 patients according to extent of disease showed 5 minimal, 85 moderately advanced, and 99 far-advanced cases of pulmonary tuberculosis and 11 patients with tuberculous pleural effusion. No instances of sickling were observed in the five patients with minimal pulmonary tuberculosis. Six of the 68 patients with moderately advanced disease had coexisting sickle cell trait, an incidence of 7.06%. Of the 99 patients with far-advanced disease, 8 had sickle cell trait, an incidence of 8.08%. One had proved sickle cell anemia. Of the 11 patients with tuberculous pleural effusion, 1 had sickle cell trait, an incidence of 9.09% (Table 1).

TABLE 1.—*Incidence of Sickle Cell Trait in Pulmonary Tuberculosis*

Classification of Disease	Patients Tested			Sickle Cell Trait			Per Cent Sickle Cell Trait
	Male	Female	Total	Male	Female	Total	
Minimal pulmonary tuberculosis	4	1	5	0	0	0	0
Moderately advanced pulmonary tuberculosis	49	36	85	3	3	6	7.06
Far-advanced pulmonary tuberculosis	56	43	99	4	4	8	8.08
Tuberculous pleural effusion	2	9	11	0	1	1	9.09
Total	111	89	200	7	8	15	7.50

No significant difference was found in the ages at which the pulmonary tuberculosis first became detected, between the patients with coexisting sickle cell trait and pulmonary tuberculosis and those with pulmonary tuberculosis alone (Table 2). Both these groups reflected the tendency for pulmonary tuberculosis to develop at a later age in Negro males than in females.

TABLE 2.—*Age at Which Pulmonary Tuberculosis Was Initially Detected*

Age, Yr.	Males		Females		Total
	Negative Sickle Cell Preparation	Positive Sickle Cell Preparation	Negative Sickle Cell Preparation	Positive Sickle Cell Preparation	
10-19	2	1	9	0	12
20-29	19	0	2	4	50
30-39	30	3	30	2	65
40-49	27	2	7	1	37
50-59	21	1	6	1	29
60 and above	4	1	2	0	7
Total	103	8	81	8	200

COMMENT

Our figures do not bear out the hypothesis that the sickle cell trait is more commonly found in tuberculous Negroes than in nontuberculous Negroes. In comparison with a previously reported [2] incidence of 12.6% sickle cell trait in 150 tuberculous Negroes, the incidence among our 200 cases was 7.5%. The incidence of the sickle cell trait among Negroes in our general hospital, outpatient, and surrounding population is 8%.† Furthermore, our study fails to show that the presence of the sickle cell trait has any significant bearing on the severity of the tuberculous disease in the lungs. There was an incidence of 7.06% sickle cell trait in our moderately advanced cases as compared with 8.08% in our far-advanced cases. Among our 15 patients with the sickle cell trait (Table 3), 6, or 40%, had moderately advanced disease; 8, or 53%, had far-advanced disease, and 1, or 7%, had tuberculous pleural effusion. In those tuberculous Negroes who did not have the sickle cell trait, 43% had moderately advanced disease,

†Watson, R. J.: Personal communication to the authors.

TABLE 3.—*Data of Patients Having Both Pulmonary Tuberculosis and Sickle Cell Trait*

	Name	Age, Yr.	Sex	Classification of Pulmonary Tuberculosis	Hemoglobin, Gm./100 Cc.	Hematocrit Value, Cc./100 Cc.	Filter Paper Electrophoresis	X-Rays of Skull, Dorsolumbar Vertebra, Hands, & Feet
1.	W. B.	30	Male	Far-advanced	14.2	43	S-A *	Negative
2.	S. M.	37	Male	Moderately advanced	11.9	34	S-A	Negative
3.	L. D.	49	Male	Moderately advanced	15.6	47	S-A	Negative
4.	J. S.	56	Male	Far-advanced	16.4	51	S-A	Negative
5.	C. W.	63	Male	Far-advanced	15.5	48	S-A	Negative
6.	W. L.	30	Male	Far-advanced	15.3	46	S-A	Negative
7.	H. W.	48	Male	Moderately advanced	15.0	51	S-A	Negative
8.	J. G.	26	Female	Moderately advanced	13.9	43	S-A	Negative
9.	A. H.	41	Female	Far-advanced	13.7	40	S-A	Negative
10.	P. B.	31	Female	Moderately advanced	11.3	38	S-A	Negative
11.	H. A.	25	Female	Tuberculous pleural effusion	13.3	42	S-A	Negative
12.	J. L.	37	Female	Far-advanced	13.9	44	S-A	Negative
13.	E. B.	23	Female	Moderately advanced	13.1	40	S-A	Negative
14.	D. N.	52	Female	Far-advanced	14.4	46	S-A	Negative
15.	R. T.	27	Female	Far-advanced	9.5	38	S-A	Negative

* Sickle (S) and normal (A) hemoglobin as shown by filter paper electrophoresis.

TABLE 4.—*Extent of Pulmonary Tuberculosis in Sickle Cell Trait and Non-Sickle-Cell Trait Patients*

	Patients, No.	Classification	Per Cent
15 cases of sickle cell trait and pulmonary tuberculosis	0	Minimal pulmonary tuberculosis	0
	1	Tuberculous pleural effusion	7
	6	Moderately advanced pulmonary tuberculosis	40
	8	Far-advanced pulmonary tuberculosis	53
184 cases of pulmonary tuberculosis without sickle cell trait	5	Minimal pulmonary tuberculosis	2.8
	10	Tuberculous pleural effusion	5.4
	79	Moderately advanced pulmonary tuberculosis	43.0
	90	Far-advanced pulmonary tuberculosis	49.0

49% had far-advanced disease, and 5.4% had tuberculous pleural effusion (Table 4).

SUMMARY

A study of 200 Negroes with pulmonary tuberculosis revealed an incidence of 7.5% having the sickle cell trait.

The incidence of sickle cell trait in the Negro population in the same area is 8%.

Neither the extent of the pulmonary tuberculosis nor the age at which it first became clinically evident was influenced by the coexistence of the sickle cell trait.

Dr. C. Hamilton provided the use of patients on his service, Mrs. Ellen Eschenbrenner did the electrophoretic studies, and Dr. R. Janet Watson gave the use of the facilities of her laboratory.

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Management of Thrombocytopenic States

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Either defect of production of platelets from the bone marrow megakaryocytes or excess of their destruction or utilization in the peripheral circulation may result in thrombocytopenia. These two basic pathogenetic mechanisms are reflected into two main types of this syndrome, amegakaryocytic and megakaryocytic (Table 1). Whatever the pathogenetic mechanism of thrombocytopenia in the individual patient may be, platelet deficiency results in serious breakdown of the hemostatic process, involving all of its phases and mechanisms[1]: *A*. The "resistance" of the vascular wall appears decreased. The tourniquet test becomes positive. *B*. The ability of the vessel to contract effectively after injury is also impaired, owing to lack of serotonin, an agent liberated by platelet disintegration. Perhaps for this reason, the bleeding time is prolonged. *C*. The fibrin clot retracts poorly. *D*. The coagulation of blood becomes abnormal, since platelet deficiency causes impaired formation of thromboplastin, and this, in turn, results in poor conversion of prothrombin to thrombin. High residual prothrombin activity in serum reflects the coagulation disturbance. These various findings in thrombocytopenia are now known to be due to the lack of individual platelet factors, whose activity involves every phase of the hemostatic process. The complexity of the hemostatic breakdown in thrombocytopenia is, perhaps, best illustrated by the practical difficulties encountered in the management of the thrombocytopenic states.

TABLE 1.—*Classification of Thrombocytopenic States*

A. Amegakaryocytic thrombocytopenia
   1. Congenital (at times neonatal)
   2. Acquired
      (*a*) Deficiency of nutritional factors (scurvy, pernicious anemia, etc.)
      (*b*) Depression of bone marrow activity by drugs (e. g., chloramphenicol)
      (*c*) Replacement of bone marrow by foreign tissue (leukemia, carcinoma, etc.)

B. Megakaryocytic thrombocytopenia
   1. Idiopathic thrombocytopenic purpura
      (*a*) Acute
         (1) Typical
         (2) Associated with hemolytic anemia
         (3) Thrombohemolytic thrombocytopenic purpura (thrombotic thrombocytopenic purpura)
      (*b*) Chronic
   2. Thrombocytopenia due to drug sensitization (allylisopropylacetylcarbamide [Sedormid], quinidine, etc.)
   3. Hypersplenic thrombocytopenia (L. E., sarcoidosis, tuberculosis, histoplasmosis, Gaucher's disease, etc.)
   4. Some varieties of neonatal thrombocytopenia
      (*a*) Due to transplacental transfer of platelet agglutinins
      (*b*) Associated with erythroblastosis fetalis
      (*c*) Due to platelet group or type incompatibility

Thus, it is not surprising that a great number of therapeutic procedures have been recommended from time to time for the treatment of the thrombocytopenic states (Table 2*A*). Some of them are controversial, like Moulten's thrombocytosin.* Others, like ascorbic acid, folic acid, vitamin B_{12}, are effective in selected situations, such as thrombocytopenia of scurvy, sprue, and pernicious anemia, respectively. Most of the remaining ones are entirely valueless. More recently, rather significant advances in the interpretation of the mechanism of bleeding in platelet

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* References 2 and 3.

TABLE 2.—*Methods of Treatment in Thrombocytopenic States*

A. The past
  1. Vitamins and nutritional factors
     Vitamin A
     Vitamin D
     Ascorbic acid *
     Vitamin E
     Vitamin P (flavones)
     Vitamin K
     Vitamin T†
     Liver extract*
     Vitamin B_{12}*
     Folic acid*
     Cobalt
     Iron
  2. Hormones
     Thyroid
     Parathyroid
     Thymus
     Diethylstilbestrol
     Progesterone
     Testosterone*
  3. Other techniques
     Moccasin venom
     Toluidine blue
     Protamine sulfate
     Thrombocytosin†
     Semicarbazones

B. The present
  1. Corticotropin and cortisone
     (*a*) To control bleeding of amegakaryocytic thrombocytopenia
     (*b*) To tide patients with idiopathic thrombocytopenic purpura over a bleeding crisis
     (*c*) In neonatal thrombocytopenia; thrombocytopenia of drug sensitization
     (*d*) To control bleeding of patients with idiopathic thrombocytopenic purpura in whom splenectomy has failed
     (*e*) To manage cases of idiopathic thrombocytopenic purpura discovered after the fifth month of pregnancy
     (*f*) To prepare a thrombocytopenic patient for splenectomy
  2. Platelets
     (*a*) In amegakaryocytic thrombocytopenia, when hemorrhage is not controlled by hormones alone
     (*b*) In idiopathic thrombocytopenic purpura, to control bleeding prior and during splenectomy
     (*c*) In all other varieties of thrombocytopenia when bleeding is not controlled by hormonal therapy
  3. Splenectomy
     (*a*) Emergency splenectomy: severely bleeding cases, poorly controlled by hormones and platelet transfusions
     (*b*) Elective splenectomy
       (1) in selected cases of amegakaryocytic thrombocytopenia
       (2) in acute idiopathic thrombocytopenic purpura when bleeding is not controlled by hormones or platelet transfusions or when no spontaneous remission occurs within six months
       (3) in chronic idiopathic thrombocytopenic purpura

C. The future
  1. Platelets
     (*a*) Availability of stable concentrates of preserved platelets
     (*b*) Development of platelet substitutes
     (*c*) Separation of platelet constituents, and their preparation from sources other than human platelets
  2. Hormones
     (*a*) Better utilization of dosage and length of treatment
     (*b*) Identification and isolation of adrenocortical hormones or hormones of other origin specifically involved in the control of vascular resistance
  3. Others
     (*a*) Inhibition of production and activity of platelet agglutinins and lysins
     (*b*) Identification of factors (nutritional, hormonal, etc.) controlling growth and activity of bone marrow megakaryocytes

* Of value in specific circumstances.
† Probably identical.

deficiency have brought a new approach in the treatment of the thrombocytopenic states. These advances include: (*a*) the appreciation of the therapeutic importance of the complex effect of corticotropin (ACTH) and cortisone on the bleeding tendency induced by thrombocytopenia; (*b*) the development of techniques for the administration of platelets; (*c*) the more complete evaluation of the role of splenectomy in various thrombocytopenic states.

Table 2*B* outlines the procedures used today for the therapy of the thrombocytopenic states. We believe that bed rest and treatment of infection have a definite role in the management of thrombocytopenia. Bed rest seems to be of importance in avoiding hemorrhagic complications such as cerebral bleeding, etc. The treatment of infection is also relevant. We have observed repeatedly that a patient with thrombocytopenia due to leukemia, for example, shows exacerbation of bleeding if stricken by infection. The reason is not clear. It is said that some bacteria may produce polysaccharides with anticoagulant effect, thus, presumably, increasing the bleeding tendency of the thrombocytopenic patient.[4]

Corticotropin, Cortisone, 17-Hydroxycorticosterone (Compound F).—The administration of corticotropin and some of the adrenocortical hormones (cortisone, 17-hydroxycorticosterone), platelet transfusions, and splenectomy represent, when properly used, methods of great efficacy in the management of the thrombocytopenic patient. The first one is very likely unspecific; the second is an example of substitution therapy. Only the third, at least in certain instances, strikes at the pathogenetic mechanism of the disease.

Corticotropin and cortisone were first shown by Robson and Duthie [5] to be useful in the control of bleeding due to increased capillary fragility. Their value in the treatment of the bleeding of practically every thrombocytopenic state can hardly be minimized. Shortly after the administration of these drugs there is a striking reduction of bleeding. The tourniquet test becomes nega-

tive in a matter of a few hours to a few days. The bleeding time may also be shortened and, finally, normalized if the treatment is continued for a sufficiently long period. Corticotropin and cortisone have an even more interesting effect in the treatment of thrombocytopenia found in certain types of leukemia. Corticotropin greatly helps to control the bleeding tendency in these conditions. In addition (noticeably in the acute and subacute lymphocytic leukemia of children), corticotropin has a direct beneficial effect on the proliferative process, especially when associated with chemotherapeutic agents. As a remission sets in, megakaryocytes are again found in the bone marrow. Thrombocytopenia is relieved and, with it, the bleeding tendency.

It is very interesting to speculate about the mechanism of hemostatic control by corticotropin and cortisone. Analytical study of the hemostatic process in patients receiving corticotropin and cortisone has shown that these drugs exhibit a multiplicity of effects. The influence on the states of the capillary wall has already been mentioned, although its mechanism remains obscure. Moreover, in many instances, the clotting time is accelerated, although no significant variations in concentration or activity of the individual clotting factors may be found. In the thrombocytopenic states corticotropin and cortisone may finally exercise another important effect directed to the platelet count. The effect of corticotropin and cortisone on the platelet count is usually negligible in the amegakaryocytic type of thrombocytopenia. In the megakaryocytic variety of thrombocytopenic purpura, idiopathic type, on the contrary, the effect of corticotropin and cortisone on the platelet count may be variable. Our experience may be briefly summarized as follows [6]: *A*. No changes in the platelet count are observed in some patients. *B*. In others, there is a slight elevation in the platelet count as long as the treatment is given and then an abrupt drop following interruption of therapy. *C*. In a third group, administration of corticotropin or cortisone is followed by return of the platelet count to normal. Most of the cases of this group, however, represented in our series, are cases of acute, self-limited thrombocytopenic purpura, in which the rise in platelet count probably followed spontaneous remission. It is open to question whether the spontaneous remission might have been accelerated by treatment. *D*. Occasionally, the administration of corticotropin or cortisone may accelerate a successful but delayed response to splenectomy. The results of corticotropin and cortisone therapy in idiopathic thrombocytopenic purpura may, apparently, vary a great deal, depending on the dose employed and the length of time administration of these drugs.[7] We have found only minor statistical differences in two series of cases, one receiving fairly low (cortisone, 1 mg./lb. [0.45 kg.] daily; corticotropin, 0.5 units/lb. daily) and the other, high doses (cortisone, 2 to 2.5 mg./lb.; corticotropin, 1 to 15 units/lb.) of these hormones for as long as two months. However, Bethell [7] obtained remissions in a majority of cases of idiopathic thrombocytopenic purpura by the use of about 300 mg. of cortisone daily for a prolonged period of time.

There are certain basic considerations related to the role of platelets in hemostasis, to the natural course of the megakaryocytic variety of idiopathic thrombocytopenic purpura, and to the variety of pathogenetic mechanisms in the disease that limit, of necessity, the absolute value of therapeutic observations. The lack of a rise in platelet count in the peripheral blood may not signify that there is or that there has been no stimulation of platelet production. The number of platelets present in the circulation does not represent the number of platelets which are produced but, rather, the balance between their production and their utilization for hemostatic purposes. Although the number of circulating platelets may not rise under therapy, many more may have been made available for hemostatic purposes. This effect might possibly be due to the postulated stimulatory effect of corticotropin and cortisone on bone marrow megakaryocytes and might explain the cessation of clinical bleeding and the improvement in the capillary

resistance. A more tangible effect on the platelet count may be expected in those cases of idiopathic thrombocytopenic purpura in which platelet deficiency is likely due to circulating agglutinins and perhaps, lysins, capable of destroying platelets in the peripheral circulation as well as at the surface of the megakaryocyte and of blocking platelet delivery from the bone marrow.† Their titer and, thus, their activity may be, if not extremely high, reduced by the administration of corticotropin or cortisone. As the activity of the platelet agglutinin or lysin is reduced, an improvement of the thrombocytopenia is likely to follow.

The results of cortisone and corticotropin therapy are usually prompt and favorable in the hypersplenic type of thrombocytopenic purpura, although the platelet count may quickly drop to a low level on suspension of therapy. Thus, corticotropin and cortisone may reduce either the platelet-phagocytic activity of the spleen or its inhibitory effect on the bone marrow. In "hypersplenic" thrombocytopenic purpura the spleen is usually, although not always, enlarged and it is easier to visualize its role in the pathogenesis of the thrombocytopenic syndrome. In the idiopathic variety, also, it appears that splenic activity may play a role in the pathogenesis of the thrombocytopenia, either by destroying platelets already damaged by circulating agglutinins and lysins or by inhibiting the function of bone marrow megakaryocytes or by sharing in the production of platelet antibodies. Thus, there are many possible mechanisms through which corticotropin and cortisone may improve the hematologic status of patients with the megakaryocytic type of idiopathic thrombocytopenia.

Whatever the mechanism of their effect, corticotropin, cortisone, and 17-hydroxycorticosterone, in that order, may find useful employment in the management of the thrombocytopenic states in general, and there are also some definite indications for their use. These are, briefly, as follows: (*a*) to manage the bleeding of the "amegakaryocytic" type of thrombocytopenic purpura; (*b*) to tide the patient with idiopathic or hypersplenic thrombocytopenic purpura and megakaryocytic drug-induced thrombocytopenic purpura over a bleeding crisis, until arrangements for splenectomy are made or until a spontaneous remission occurs; (*c*) to control bleeding in most types of neonatal thrombocytopenia; (*d*) to manage the critical patient with chronic thrombocytopenic purpura in whom splenectomy has failed. Severe bleeding which occurs either at the time of menstrual bleeding, usually severe and protracted in these cases, or at any other time may often be controlled well by the intermittent use of corticotropin or cortisone; (*e*) to manage the bleeding of pregnant women with thrombocytopenic purpura when the disease is discovered or becomes clinically manifest after the completion of the fifth month of pregnancy; (*f*) to prepare a patient for splenectomy in conjunction with or without the use of platelet transfusions. Use of these drugs has virtually eliminated "emergency" splenectomy, since clinical bleeding can usually be controlled well with their use. The patient is treated for a few days prior to surgery with average doses (cortisone, 1 mg./lb. daily; corticotropin, 0.5 units/lb. daily). After surgery, treatment should be gradually withdrawn (in 3 to 5 days), to prevent, on one hand, adrenocortical crisis following too prompt withdrawal of the drug or, on the other hand, administering these drugs as the platelet count rises to high levels. A combination of the effects of splenectomy on the thrombocyte count and the continued administration of corticotropin and cortisone would be likely to result in thromboembolic complications.

Benefits of hormone therapy are even more evident in the acute type of idiopathic thrombocytopenic purpura. The bleeding in this variety of the disease is acute only in the first few days and can then be usually controlled by corticotropin or cortisone. Later the bleeding abates spontaneously and one can well wait for the occurrence of a spontaneous remission, which is seen in 7 to 8 out of 10 cases in from three weeks to six months.

† References 8-11.

Transfusion of Platelets.—Transfusion of platelets is now becoming a routine procedure in some institutions, and it is likely that it will be of general use in the not-too-distant future, as the gap between the laboratory and clinical practice is being progressively filled.‡ The ultimate, routine use of platelet transfusions will depend, in the last analysis, on the successful solution of four major problems: (*a*) how to collect blood with optimum preservation of platelets; (*b*) how to separate them rapidly and completely from other formed elements of the blood, whose enzymatic activity may injure platelets and thus reduce their viability and therapeutic effectiveness; (*c*) how to preserve platelets in vitro without damage to their physiological properties, thus increasing the possibility of their general use and transportation where no facilities exist for their collection; (*d*) how to transfuse them into the recipient without loss. The first and last problems have been solved in part by careful study of the factors which induce loss of platelets during collection and manipulation.[12] Several factors cause destruction of platelets during collection and administration of blood, such as the collection of blood in a vacuum bottle (where foaming occurs, almost without exception), the contact with glass surface, and/or poor or delayed mixing with the anticoagulant solution at the time of the collection of blood. Accordingly, the best platelet transfusion technique is the direct transfer of platelet-rich blood (preferably polycythemic) from the donor to the recipient. This can be accomplished with either of two techniques: (*a*) a closed system which has been treated with silicone or an oil-soluble quaternary ammonium compound (Arquad 2-C) for the glass or metal parts, respectively; (*b*) an open system, using silicone-coated syringes and Arquad 2-C-coated needles (Fig. 1).

More practical are the techniques employing indirect transfusion of platelet-rich blood which are of special value in patients with marked anemia. Blood is collected by gravity in entirely plastic systems (plastic bags) or in systems which have been made water-repellent by coating glass with silicone or needles with Arquad 2-C (Fig. 2*A* and *B*). The choice of the anticoagulant also is not without effect in determining the optimal recovery of platelets. Heparin is a poor anticoagulant for this purpose. Ordinary acid citrate dextrose (ACD) solutions are preferable but not ideal. Edathamil disodium (EDTA-Na_2; Sequestrene-Na_2) § in 0.1% concentration appears to be the best anticoagulant for optimal collection of platelets. Treatment and preservation of the packed red cells will be described elsewhere. With these techniques the preservation of the largest number of platelets (at least 85%), during collection and administration to the recipient, is assured especially if only nylon filters are used or, better still, if filters are entirely eliminated.

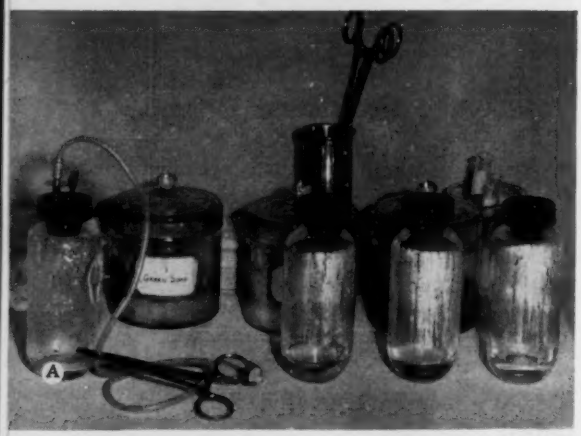
The loss of platelets during collection and administration is minimal with the techniques previously mentioned, since manipulations are limited. There are, however, several instances in which the patient requires selectively platelets and not red cells, since there is no anemia and transfusion of whole blood would cause plethora. A typical example is the patient with idiopathic thrombocytopenic purpura being readied for splenectomy, who usually has no anemia; another is the patient with aplastic anemia whose need for red blood cells has already been fulfilled but who, nevertheless, still requires platelet transfusions for the control of bleeding. When separation of platelets from other elements of the blood becomes necessary, the manipulations required for this purpose appear to affect to a small extent the recovery but to a great extent the viability of platelets.

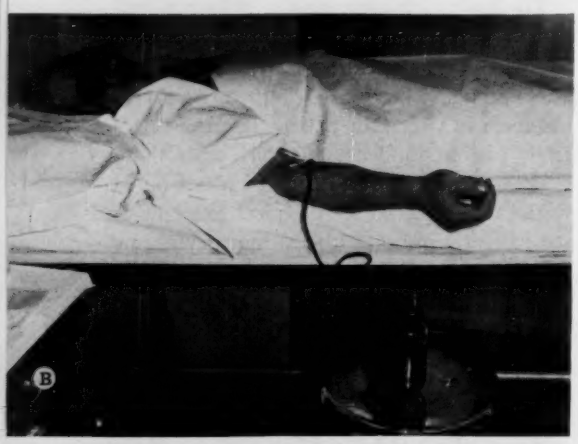
‡ There are several techniques recommended for platelet collection and separation (References 12, 13, and 14). The discussion, however, will be limited to those procedures which can be followed by those who are supplied with a minimum of equipment and facilities.

§ Disodium ethylenediamine tetra-acetate dihydrate. The anticoagulant solution has the following composition: EDTA-Na_2 1.0 gm.; NaCl 0.7 gm.; distilled water to 100 ml.; nine volumes of blood are added to one volume of the solution.

Fig. 1.—Techniques of platelet transfusions: direct transfusion technique. Syringes are coated with silicone, and needles are coated with Arquad 2-C. Blood is collected in syringe from the donor through a No. 15 gauge needle, transferred directly to the recipient through a No. 18 gauge needle. Fresh syringes are used every time, if possible; if not, they are rinsed with 0.2 M solution of sodium citrate between times.

No ideal system exists allowing the separation of platelets from the other formed elements of the blood. The simplest and, perhaps, best method at the present time consists in the separation of platelet-rich plasma from red cells by slow centrifugation. Speed and times of centrifugation vary from case to case, depending on the volume of blood centrifuged and on the hematocrit value of the donor.‖ Preparations of plasma rich in platelets are thus easily obtainable, although with about 2 to 10% contamination with red and white blood cells (Fig. 2*A-E*). This technique can be done with either silicone-coated bottles or plastic containers (plastic bags). In the first instance, platelet-rich plasma is transferred to another silicone-coated bottle by gentle suction through plastic tubing. In the second instance, the





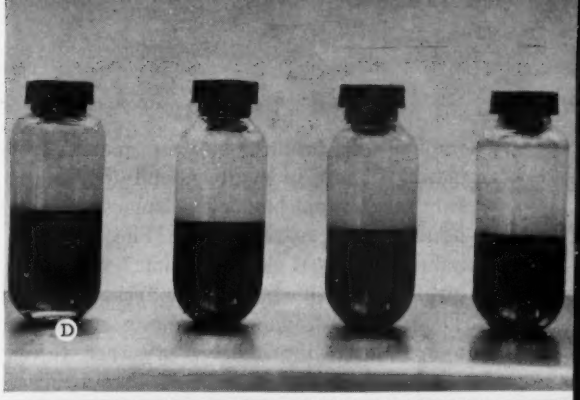
‖ An average speed of 1500 rpm for 20 minutes usually produces satisfactory separation of red blood cells and platelets. These remain in the supernatant plasma.

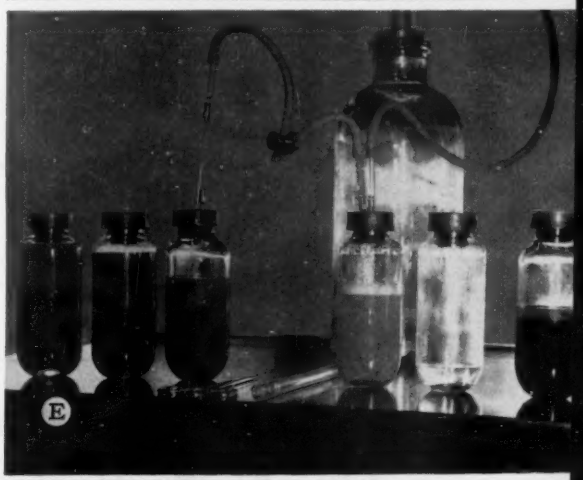
Fig. 2.—Techniques of platelet transfusions: preparation of platelet-rich plasma and platelet concentrates. *A*, 250 ml. bottles are made ready for collection of blood. Each is coated with silicone and contains 25 ml. of disodium edathamil 1% solution. Vacuum is exhausted and blood is collected through a plastic tube connected with two Arquad 2-C-coated needles. *B*, blood is collected by gravity, avoiding foaming as much as possible and without stasis. *C*, 900 ml. of whole blood is collected from two compatible donors in 100 ml. of 1% disodium edathamil solution. *D*, bottles are centrifuged at 1500 rpm for 20 minutes at 4 C. Platelet-rich plasma is thus separated from red blood cells and most of the white cells. *E*, platelet-rich plasma is separated by gentle suction through plastic tubing (protected, in the figure, by rubber tubing) into empty silicone-coated containers. *F*, platelet-rich plasma may be transfused as such, or it is centrifuged at 3000 rpm for 30 minutes at 4 C. If desired, platelets may be washed free of plasma by resuspending them in saline containing 2% Triton WR-1359 and packing them down by centrifugation repeatedly, The final step is the resuspension of the platelet button in either a small volume of saline solution or one of the many preservative solutions (see text). *G*, the final products of this technique: red cells, plasma, platelet suspension.

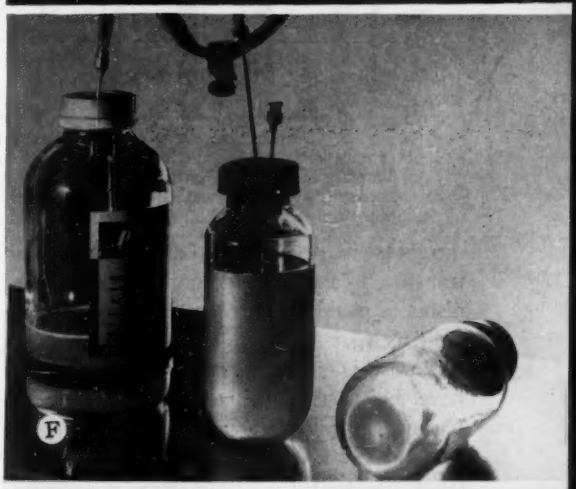
supernatant plasma is transferred to another plastic container [15] by gently squeezing the bag from the bottom up after the two are connected with a plastic system.

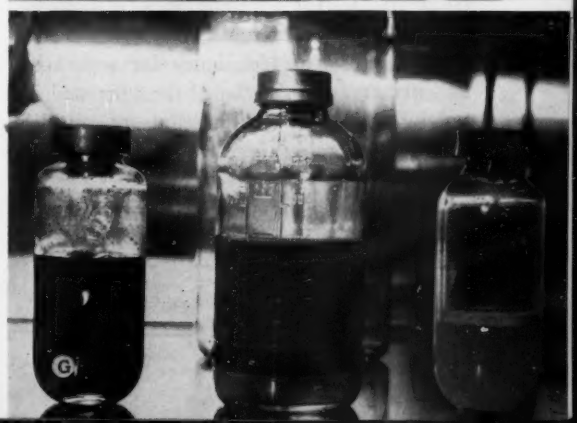
In some instances, especially for thrombocytopenic patients being prepared for surgery, one may wish to use concentrates of platelets, and so a large number of thrombocytes, separated from red and white cells and plasma, may be administered in a small volume of saline solution or other suspending medium. Large volumes of blood must be used, because considerable loss of platelets follows the necessary repeated centrifugations. The technique used, a modification of that suggested by Minor and Burnett,[16] is described in detail in Figure 2*A-G*. To prevent platelet agglutination or disintegration during the intermediate steps of separation and washing, surface-active agents like sorethytan (20) monooleate (Tween 80) and an oxyethylated tertiary-octylphenol-formaldehyde polymer (Triton WR-1339) should be employed. These agents, however, should not be used in the final medium, since they possess moderate hemolytic activity in vivo. In the preparation of platelet concentrates with this technique plastic bags can be used as well as silicone-coated bottles. Plastic containers have the advantage that the separation of plasma and of washing fluids from platelets can be achieved without aspiration but, rather, by gentle pressure on the bag as described.

It is clear however, that platelet transfusions will not gain their rightful place in the management of thrombocytopenic states until platelets can be preserved and made immediately available when required. This problem is far from solved, owing, partially, to the difficulty in separating platelets from other formed elements of the blood without fairly large loss and, partially, to the limited knowledge of the metabolic requirements and metabolic activity of platelets; consequently, an ideal medium for preservation remains to be found. After platelets have been separated and suspended in plasma, a striking dissociation of their hemostatic properties takes place. They remain capable of causing con-









version of prothrombin in platelet-free plasma almost indefinitely, and they show only minor morphologic changes over a period of one to two weeks. The ability of inducing optimal clot retraction however, is lost in a very short time (one to three days). These changes are more striking and occur more quickly if platelets have been resuspended in saline solution or other artificial media rather than plasma. Together with the impairment of their hemostatic properties in vitro there is, in preserved platelets, a striking decrease in their survival in vivo. Platelets injected directly as platelet-rich blood into patients with amegakaryocytic thrombocytopenia, who have never been transfused (and, thus, do not possess mechanisms of platelet destruction), survive for as long as four to five days. Their survival, however, is strikingly reduced if platelets have been separated and resuspended in plasma prior to their administration to the recipient. Practically no elevation of platelet count follows the administration of platelets suspended in saline solution or other media. Thus, all known techniques for separation and preservation developed thus far and involving repeated manipulations of platelets, affect unfavorably their survival or viability in vivo.

It seems important at this point to establish a clear distinction between "recovery," viability, and "hemostatic function" of platelets. "Recovery" is the percentage of platelets originally present in blood which are recovered in the final preparation. As shown in Figure 3, recovery is usually high with any of the techniques. There is, perhaps, one exception: the technique of separation of platelets from other formed elements of the blood by trapping on ion-exchange resins.[17] Recovery in this instance is never higher than 40% to 70%. "Viability" is the ability of platelets to survive and be counted in the peripheral blood after their administration to patients with amegakaryocytic thrombocytopenic purpura never previously transfused. As mentioned already, viability is strikingly reduced by any procedure involving manipulation (centrifugation) of platelets. Although good viability is important for maximum therapeutic effect, there is no absolute relation between viability and "hemostatic effectiveness". Thus, all platelet preparations, provided they are not stored over a period of six months to two years, exercise some control on thrombocytopenic bleeding, primarily because they all contain, no matter what the status of preservation of platelets, stable chemical constituents supplied by thrombocytes capable of normalizing some of the phases of the hemostatic mechanism in the thrombocytopenic patient. So important is the hemostatic effect of platelet

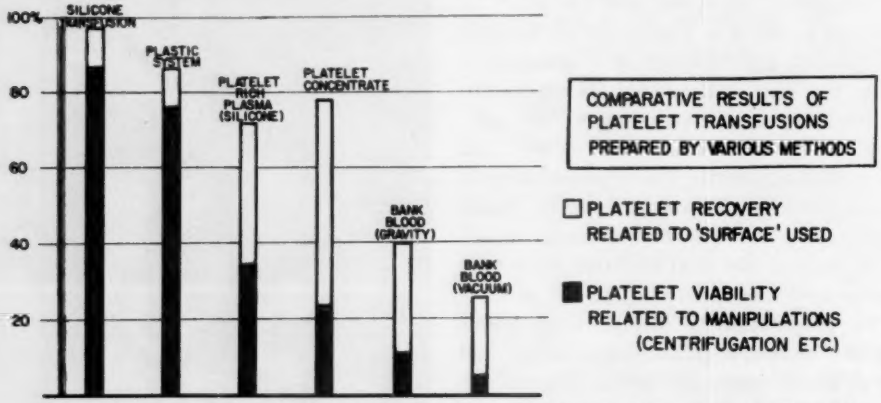


Fig. 3.—Platelet "recovery" and platelet "viability." The length of the column indicates the percentage of recovery; the black part, the percentage of viable platelets. It appears that recovery of platelets is dependent on the method of collection and the nature of the surface used. Viability is apparently more dependent on the amount of manipulation. It will be remembered that viability only partially influences the hemostatic effect of platelets (see text).

products that platelet transfusions are beneficial, to various degrees, in the control of bleeding even when platelets fail to survive in the patient's circulation or, as in many cases of idiopathic thrombocytopenic purpura of the chronic variety, when there are demonstrable platelet-destruction mechanisms in the patient's circulation. Obviously, this consideration emphasizes the importance of preserved platelets in the management of thrombocytopenic states. It also justifies the continued search for a suitable platelet-preservation medium. Like Tullis,¶ we have tried a large group of media, with generally limited success. More recently we have used, with better results in a limited series of cases, platelets preserved in media containing, in addition to dextrose and electrolytes, 2% glycerin and 0.15 M cysteine.#

Perhaps of even greater limitation to the therapeutic efficacy of platelet transfusions is the disease state of the patient receiving them. Optimal results are obtained in cases with the amegakaryocytic type of thrombocytopenia, since these patients, if not transfused previously, present no evidence of platelet-destruction mechanisms. In this ideal condition, the effect of the transfusion of platelets (especially if viable) on the hemostatic defect of the thrombocytopenic patient is indeed striking. If, for example, one such patient receives a direct transfusion of platelets with siliconized apparatus, not only is the hemorrhagic tendency well controlled for five to seven days but the platelet count in the patient also remains elevated for three to five * days and bleeding time and capillary fragility are improved.† Significantly, and perhaps again indicating the hemostatic value of platelet products, the improvement in bleeding time and capillary resistance may persist for 26 to 72 hours after the platelet count has fallen to pretransfusional level. While the platelet survival is much shorter or even fails to materialize when platelets suspended in plasma or washed platelets are given, the hemostatic effects are only moderately less. Results are less satisfactory in patients with the hypersplenic or the idiopathic variety of thrombocytopenic purpura (in which a platelet-destruction mechanism is often demonstrable) and in secondary thrombocytopenia when the patient has received multiple platelet transfusions.‡ In the latter instance, a mechanism of platelet destruction develops secondarily as a result of platelet isoimmunization and makes platelet transfusions progressively less effective. In both instances, the effect of the transfusion on the hemostatic abnormalities and on the clinical bleeding is only moderate, and a large number of platelets (platelet concentrates, preferably) are required to obtain a fairly satisfactory clinical effect.

In view of the practical difficulties still encountered in the preparation and supply of platelet suspensions and in view of the evidence that transfusions of incompatible platelets quickly decrease the effectiveness of platelet transfusions in the recipient, it is important that indications for platelet transfusions be clearly established and that these be limited to patients in whom control of bleeding cannot be achieved with other modalities alone (corticotropin, etc.). Our experience would suggest the following conclusions: *A.* in amegakaryocytic thrombocytopenia platelet transfusions should be limited to those cases in which there is impending danger of serious internal hemorrhage or where in which corticotropin and cortisone fail to control bleeding. The indiscriminate administration of platelets to these patients renders valueless in a short time a

¶ References 13 and 14.

Stefanini, M.: Unpublished data.

* A notable exception is represented by cases of metastatic carcinoma with amegakaryocytic thrombocytopenia induced by infiltration of the bone marrow by malignant cells. Perhaps owing to antigenic stimulation of the cancerous cells, a platelet antibody is found very rarely in these patients, which may contribute to the pathogenesis of their thrombocytopenia and also strikingly decrease the survival time of viable platelets injected in the patient's circulation (Stefanini, M.: *Fed. Proc.*, to be published).

† References 18 and 19.

‡ References 20-22.

therapeutic measure which should be used only in the nature of an emergency and which, when so used, is of extreme value. *B.* In idiopathic thrombocytopenic purpura platelet transfusions should be used only to control severe bleeding or just prior to and during splenectomy. In both cases administration of corticotropin and cortisone appears to enhance the hemostatic effect of platelets. As a large number of platelets is required and these patients often exhibit platelet-destruction mechanisms, one should try to administer many platelets in a short period of time. Platelet concentrates obtained from 2 to 4 pt. (0.95 to 1.90 liters) of blood are particularly effective. With these techniques, splenectomy has become a practically bloodless procedure. *C.* Additional indications for platelet transfusions include all patients with thrombocytopenia, of any nature, when bleeding has failed to respond to other therapeutic procedures. These conditions include thrombocytopenic purpura due to drug sensitization, thrombocytopenia in the late period of pregnancy, congenital and neonatal thrombocytopenia, and chronic thrombocytopenic purpura which has failed to respond to splenectomy.

Splenectomy.—Because, of these developments, and because of striking advances in surgical and anesthesiologic techniques, splenectomy in thrombocytopenic states no longer represents a technical problem. Splenectomy may find indications in cases of amegakaryocytic as well as megakaryocytic thrombocytopenic purpura. Especially in the first instance, the selection of patients who may benefit from the procedure is not an easy one and can be decided upon only after careful evaluation of the patient's status. It may be stated in somewhat general terms that splenectomy may be of value in carefully screened cases of amegakaryocytic thrombocytopenia due to leukemic processes or aplastic anemia. Splenectomy is more likely to be relatively successful if the organ is enlarged or if complications are present which suggest hypersplenism, like hemolytic anemia. It is not rare to see an elevation of the platelet count follow splenectomy in these patients and contribute substantially to the control of bleeding, at least for a few months. Splenectomy is also indicated in some cases of congenital amegakaryocytic thrombocytopenia.

Indications for splenectomy are better defined in the megakaryocytic type of thrombocytopenic purpura. Necessity for operation is obvious in the "hypersplenic" type of thrombocytopenia. In idiopathic thrombocytopenic purpura, splenectomy is no longer an indiscriminate procedure. The introduction of corticotropin, cortisone, and platelet transfusions has greatly limited the indications for "emergency" splenectomy. As already mentioned, severe bleeding in the acute variety of idiopathic thrombocytopenic purpura or in the acute relapse of the chronic type of the disease is self-limited. It can usually be controlled by the use of platelet transfusions and corticotropin and steroid hormones. Later on, bleeding ceases, and no further treatment is indicated in many instances, and it becomes possible to wait for spontaneous remissions, very likely to occur in the acute type of the disease (especially in children) or to prepare the patient for surgery under favorable conditions. This should not be interpreted to mean that "emergency" splenectomy is never to be done. It has an indication, for example, in the adult whose bleeding is very severe and poorly controlled by corticotropin, cortisone, and platelet transfusions, since under these conditions cerebral bleeding is a distinct possibility. Splenectomy is also indicated when facilities for platelet transfusions are not available and there are cogent reasons prohibiting or limiting the full use of corticotropin and cortisone. Otherwise, it seems unjustified in view of the risks involved. Operation is definitely contraindicated in idiopathic thrombocytopenic purpura of the newborn and in purpura of drug sensitization. The first is almost always self-limited, the second remits promptly as soon as the level of the offending drug in blood has fallen below the initial level.

Once the acute bleeding is over, further conduct of therapy must again be carefully

individualized. If the case is of the acute variety, especially in children, as already mentioned, one should wait for spontaneous recovery, which may occur at any time within three weeks to six months, or even later. Corticotropin or cortisone may be administered if new bouts of bleeding are noted. If, however, serious bleeding reoccurs (as is very seldom seen) or if the patient presents signs of cerebral bleeding, it is hazardous to wait. Splenectomy, as mentioned, should also be done for those patients whose symptoms suggest initially idiopathic thrombocytopenic purpura of the acute variety but whose platelet level fails to reach normal within four to six months. When there is a definite history of remissions and relapses, as is typical of the chronic variety of idiopathic thrombocytopenic purpura, or when there are other findings which suggest that the disease is of the chronic variety,[24] splenectomy is the treatment of choice. Splenectomy is also indicated in idiopathic thrombocytopenic purpura during the first five months of pregnancy regardless of its variety. The operation tries to achieve the double goal of protecting the mother against bleeding during the rest of pregnancy and delivery and of limiting the severity of the effects of the thrombocytopenia which may be present in the child at birth. It is agreed that although splenectomy may induce hematologic remission in the mother the child may still be born thrombocytopenic.[25] However, the bleeding tendency is usually mild and of short duration in the thrombocytopenic child of a splenectomized mother. This appears to be true even if splenectomy failed to induce hematologic recovery in the mother.

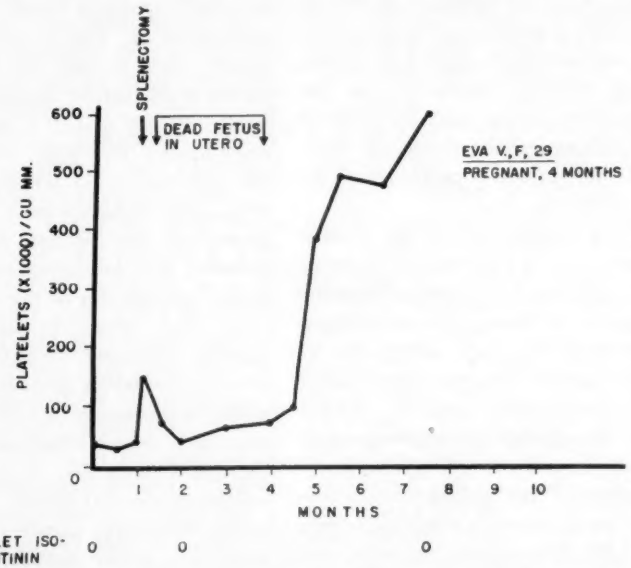


Fig. 4.—The complexity of factors determining the end result of splenectomy in idiopathic thrombocytopenic purpura. The patient, a 29-year-old, four-month-pregnant woman, was first seen complaining of diffuse petechiae and ecchymoses. A diagnosis of idiopathic thrombocytopenic purpura was made; splenectomy was advised and performed elsewhere. Splenectomy was followed by improvement of the bleeding manifestations and by minor and fleeting elevation of the platelet count. It was found soon afterwards that the fetus was dead in utero. There was however, improvement in the bleeding manifestations. Spontaneous delivery occurred at the end of the ninth month of pregnancy. The platelet count began to rise a few days later, and complete hematologic recovery followed.

Remission may be induced by splenectomy in idiopathic thrombocytopenic purpura by a variety of mechanisms. First, the spleen exercises a powerful, yet undefined inhibitory influence on the bone marrow, and its removal might increase the production and delivery of platelets from the megakaryo-

cytes. A second consideration regards the ability of the spleen to sequester and destroy, or lyse, normal platelets as a major factor in the pathogenesis of idiopathic thrombocytopenic purpura. While this appears doubtful, the spleen may be a selective graveyard of platelets in a special type of idiopathic thrombocytopenic purpura. As mentioned, platelet agglutinins and lysins are found in the plasma of approximately 50% of patients. It is postulated that when agglutinins are present the spleen removes platelets which have been damaged by the antibody.§ Thirdly, removal of the spleen may reduce titer and activity of platelet agglutinins and lysins, which are very likely produced in part by the spleen. Finally, interaction of the activity of the spleen and of other less-defined pathogenetic factors may be extremely complicated and offer unsolved problems of interpretation (Fig. 4).

Whatever the mechanism of its success may be, splenectomy is followed by recovery in 6 to 7 out of 10 cases of chronic idiopathic thrombocytopenic purpura. This recovery is usually permanent, although when platelet agglutinins are present they may persist after splenectomy. Occasionally, also, the platelet count may be found slightly and temporarily depressed as these patients suffer from intercurrent infections. When splenectomy is successful, the platelet count rises to high values, in order of 1,000,000/cu. mm. or more, and then, in the space of three to four weeks, slowly returns to normal. Failure of splenectomy may take a number of ways. The platelet count may (*a*) rise to high values immediately following splenectomy and drop again to preoperative levels in a few days or weeks; (*b*) rise to normal or subnormal levels and quickly drop to low values again; (*c*) fail to rise altogether ‖; (*d*) rarely, remain normal for a number of months or even years and then drop again to low values. The management of the cases of idiopathic thrombocytopenic purpura which fail to respond to splenectomy has been discussed previously.

It is unfortunate that the result of splenectomy is entirely nonpredictable in a given case of idiopathic thrombocytopenic purpura. A number of criteria have been suggested from time to time, to help predict which cases of the disease will respond to surgery. There is a widely shared idea that prompt elevation of the platelet count to values over 1,000,000/cu. mm. (by direct count) suggests permanent remission. This is usually, but not constantly, true. It has also been stated that presence of platelet agglutinins in the patient's plasma makes a successful splenectomy likely.[9] This point of view is based on the observation, in which we concur, that when agglutinins are present in the patient's circulation the spleen removes damaged platelets, thus becoming an important factor in the pathogenesis of the thrombocytopenia. Once the spleen is removed, platelets, although damaged, should be able to remain in the circulation and exercise at least a moderate hemostatic effect. There are, however, two major objections to this line of thought. One is that other provinces of the reticuloendothelial system, besides the spleen, may well remove platelets from the circulation, this action probably becoming more significant after splenectomy. The second consideration involves the nature of the antiplatelet agents found in the circulation of patients with idiopathic thrombocytopenic purpura. In many instances, the agent is a platelet lysin as well as a platelet agglutinin and is capable of destroying platelets without assistance from the spleen. Thus, although the splenic tissue participates in the production of the platelet lysin, its removal can hardly be expected to cure the thrombocytopenia, especially if the titer of the lysin is high. Our own experience seems to support the opposite point of view, that presence or absence of platelet agglutinins is not predictably related to the success or unsuccess of splenectomy.[20] It is fortunate, however,

§ References 9 and 11.

‖ Failure to respond promptly to splenectomy does not necessarily indicate failure, since we have seen cases in which the platelet count began to rise and stabilized at normal levels days or even a few weeks after the operation. These cases may well be examples of the acute variety of the disease mistakenly diagnosed as chronic, in which a late spontaneous remission developed.

that although splenectomy may fail to raise the platelet count permanently it is usually followed by improvement in the bleeding tendency.

Patients who responded to splenectomy only to relapse after a varying interval of time, as well as those who experience only a partial response, raise an additional problem, that of the significance of "accessory spleens." There is no question that accessory spleens should be carefully searched for at the time of surgery, even in sites like the parametrium, Douglas' pouch, etc. which are usually overlooked. However, when relapse occurs very shortly after splenectomy and a careful search for accessory spleens was conducted at operation, further surgery is probably fruitless and unadvisable. When, on the other hand, relapse occurs years after splenectomy, the presence of undetected accessory spleens which have taken over the function of the main organ should be given consideration. Consultation with many surgeons and hematologists, however, seems to emphasize the rarity with which accessory splenic tissue is found in relapsed cases of idiopathic thrombocytopenic purpura. This conclusion is supported by observations of Loeb and co-workers.[27] These authors used thorium dioxide solution (Thorotrast) in an attempt to demonstrate accessory splenic tissue. No evidence of this was found in a small series of cases of relapsed idiopathic thrombocytopenic purpura.

What in the Future?—While the various therapeutic procedures outlined here represent considerable progress, they have limitations which have become apparent in the course of this discussion and hardly need to be emphasized. It would, perhaps, be logical at this time to consider whether any significant progress may be expected in the near future.

Some of the progress in this field will undoubtedly come from a better use of the therapeutic means available today. Satisfactory platelet concentrates may soon become available with the progressive improvement of preservation techniques. Much remains to be learned with regard to the choice of proper dosage and duration of corticotropin and cortisone therapy in thrombocytopenic states. Moreover, it is possible that adrenocortical hormones other than cortisone and 17-hydroxycorticosterone may be more specifically involved in the control of vascular resistance, since corticotropin appears to be often more active than cortisone. Identification of these hormones may supply another important tool in the control of thrombocytopenic bleeding.

More worthy of discussion, although this is of necessity speculative, are the future possibilities of treatment in idiopathic thrombocytopenic purpura. It appears that platelet agglutinins and lysins may be responsible for the thrombocytopenia of some cases of the disease. It may become possible perhaps, to inhibit their production by the tissues and also their activity. Another aspect which is almost completely unexplored is the control of growth and activity of bone marrow megakaryocytes by nutritional and hormonal factors and the possible role of these factors in the pathogenesis of idiopathic thrombocytopenic purpura.¶ It is conceivable that agents capable of stimulating megakaryocytic proliferation and function may be of use in the treatment of idiopathic thrombocytopenic purpura. Finally, additional hope for the practical management of the thrombocytopenic states is offered by the use of separated single platelet factors and by the development of platelet substitutes. Platelet thromboplastic factor and serotonin (5-hydroxytryptamine) have recently been used to control bleeding due to platelet deficiency. Both appear to exercise generally good con-

¶ Complete ignorance of factors regulating production and delivery of platelets from the megakaryocytes is well illustrated by the following observation. A patient with idiopathic thrombocytopenic purpura had been splenectomized one year prior to admission, with temporary good result and relapse. Laparotomy failed to reveal accessory spleens, but, following operation, the platelet count rose to a high level for a few days and fell quickly again to preoperative values. Parenteral administration of epinephrine (Adrenaline) hydrochloride (0.5 ml. of 1% solution) at a later date was followed, in the same patient, by elevation of the platelet count to normal values for three days.

trol of bleeding, although laboratory studies indicated that their action is limited to return to normal prothrombin consumption during clotting and bleeding time. Another possibility, that of obtaining individual platelet factors from sources other than human platelets, such as bovine platelets or entirely from the "laboratory shelf," should not be minimized as a reality of the future.

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Rheumatic Restenosis of Mitral Valve

Report of a Case with Death Almost Five Years After Mitral Valvulotomy

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In the patient whose case is reported here restenosis, almost certainly on a rheumatic basis, was confirmed by necropsy. Factors in the restenosis are evaluated.

Certain rheumatic restenosis of the mitral valve, although much feared, has been adequately documented in very few cases. In the patient of Donzelot and his collaborators [1] rheumatic activity was thought to have been present at the time of operation. Auscultatory signs of mitral obstruction and respiratory distress reappeared, and the patient died less than one month after mitral valvulotomy. Autopsy revealed "reconstitution of the mitral stenosis." Brock [2] referred to a patient in whom restenosis had occurred by two years after operation. In two patients, who died three weeks and seven months after operation, Muller [3] found no sign of restenosis. Wood [4] stated, without detailed amplification, that in an extensive experience restenosis occurred in 5% of patients. However, he pointed out that in the first 20 patients operated on 3 instances (15%) of restenosis occurred. The last finding had at least two alternative explanations. It may indicate that sufficient time has not elapsed to permit true appraisal of the risk of restenosis. On the other hand, it may indicate that the early cases were more likely to be operated on in spite of signs of rheumatic activity, that obstruction was not relieved as adequately as is now practiced, and that prophylaxis against streptococcal infections was not as generally employed.

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F. C. (J. H. H. 493563), a white woman, was born in 1918. The mother suffered from hypertension and died after a stroke at the age of 56 years.

The patient had many so-termed "growing pains" as a child. She was also said to have been a diphtheria carrier. For about two years, between the ages of 8 and 10 years, she was chronically although intermittently ill with mild polyarthritis, recurrent fever, and headaches. Since junior high school the patient had been aware of a "funny beat" of the heart. Tonsillectomy and adenoidectomy was performed in 1936. To her knowledge rheumatic heart disease was not detected until 1943. Over the years there was progressively increasing exertional dyspnea. Between 1947 and 1949 four episodes suggestive of minor cerebral embolization occurred; certain differentiation from hysteria is difficult. She was forced to stop work as a night-club entertainer because of increasing exertional dyspnea.

The patient was first seen at this hospital March 17, 1949. At that time she would become dyspneic from walking any distance at all on the level, and stairs had become almost impossible. She slept on two pillows. Ankle edema had been conspicuously absent.

The patient was a somewhat pale thin young woman who could lie flat without discomfort. The only findings of note were related to the cardiovascular system. At the apex there was a definite diastolic thrill synchronous with the subsidence of a localized lifting apical systolic impulse. The rate was rapid, and the rhythm was totally irregular. The heart was enlarged to the left anterior axillary line by percussion, and the midportion of the left border of dullness was full. The second pulmonary sound was accentuated. A soft high-pitched diastolic murmur was audible at the left sternal border. At the apex the first sound was very loud and snapping. There was no definite systolic murmur. The second sound was followed by an opening snap. Beginning immediately with the opening snap a

murmur of the quality typical of mitral stenosis occupied approximately two-thirds of diastole.

The liver descended 1 cm. below the costal margin on deep inspiration. There was no peripheral edema. Peripheral pulses were all normal. No abnormal neurologic signs were detected.

In March, 1949, the patient was given prophylactic sulfadiazine, 0.5 gm. twice a day, and remained on this treatment in a virtually uninterrupted course until her death, five and one-half years later.

On Nov. 12, 1949, the patient applied to the accident room because of acute pulmonary edema which developed following a walk of several blocks. When seen in the clinic a few days later she reported occasional feelings of feverishness and several epistaxes. The liver edge extended half way to the umbilicus. At the base of the nail of the left index finger a pin-point hemorrhage was seen. There was a bruise on one arm.

operator could not be certain of tearing of the medial commissure. (As described below, subsequent autopsy examination did reveal a scar of the medial commissure area, where tear was probably produced at operation.) No calcification was felt, but the valve was obviously stiffened and thick. The auricular appendage amputated at operation was by error discarded before histological examination.

The patient pursued an entirely satisfactory postoperative course. There was never evidence of activation of rheumatic fever above the level indicated by the several measurements listed above.

In the few months after operation there never was any doubt of subjective improvement of considerable degree. She was able to walk as much as two miles in a cold wind without dyspnea. Although no diastolic rumble was heard while she was in the hospital, it was always heard on clinic visits. However, during the few months immediately after val-

Data from Cardiac Catheterization

	Jan. 5, 1950	April 3, 1950	April 28, 1953
Cardiac output			
Rest	2300	2670	(Unsatisfactory because of pulmonary edema)
Exercise	4110	3780	
Pulmonary arterial pressure			
Rest	84/46 (mean 63)	59/32 (mean 41)	86/42 (mean 57)
Exercise	108/65 (mean 80)	26/10(?) (mean 15)	
Pulmonary capillary pressure			
Rest	32	32/26	27
Exercise	47(?)	.....	.....
Maximum pulmonary resistance (rest)	42.5	23.8	.....
Pulmonary arteriolar resistance	20.8	7.0	.....

The patient was admitted to the hospital on Dec. 13, 1949. Cardiac catheterization was performed on Jan. 5, 1950, with the results indicated in the Table. Mitral valvulotomy was performed on Jan. 23, 1950. During the period of observation before operation the white blood cell count was over 10,000 in four of seven determinations (highest, 14,840); the hematocrit value was always in the vicinity of 44%, and the sedimentation rate (Wintrobe) was elevated to the vicinity of 30 mm/hr. on the six determinations. Elevations of rectal temperature to 100 F or slightly more occurred almost daily.

Operation was performed on Jan. 23, 1950, by Dr. Alfred Blalock. This was the third mitral valvulotomy performed in this hospital. The left atrium was entered in the customary manner via the auricular appendage. The mitral orifice was about one-half to one-third the size of the end of the operator's index finger. The finger was pushed through the valve orifice with easy tearing of the lateral comissure where adhesion of the cusps was thinnest. The

vulotomy, the diastolic murmur seemed much less prolonged and loud, being limited to early diastole. No definite systolic murmur was heard. The diastolic murmur at the left sternal border, interpreted as a Graham Steell murmur, was usually audible. The opening mitral snap was if anything more striking. In May, 1950, the patient reported walking five miles without dyspnea. Repeat cardiac catheterization on April 3, 1950 (Table), appeared to afford objective evidence of improvement.

The liver remained enlarged. The spleen was never felt in this patient. A few examiners who thought they felt the splenic tip may have been feeling the enlarged left lobe of the liver. The patient was seen at about three-week intervals during 1950. Progressive increase in the diastolic rumble was recorded. By Nov. 9, 1950, it was recorded that "the apical diastolic is now as loud and rumbling as ever!" During that year the patient reported occasional sweats at night. On one occasion a black-and-blue area developed on the dorsum of the left thumb

after a sudden pain "like something hitting the thumb." In August the white cell count was 11,000; sedimentation rate, 12 mm., and hematocrit value, 45.8% on one testing. In December, 1950, she was hospitalized for eight days because of fever and increasing dyspnea. Her sedimentation rate and white cell count were consistently elevated during that admission. She received 4.0 gm. of chlortetracycline (Aureomycin) a day for four days. No β-hemolytic streptococci were discovered on that and other occasions.

During 1951 the liver was enlarged each time the patient was examined, and often considerable discomfort, presumably related to the hepatomegaly, was present. The patient felt very tired much of the time, and she frequently called attention to "splinter hemorrhages" in the nail beds. At least one episode of sore throat prompted the administration of penicillin by her local physician. By July, 1951, diuresis with mercaptomerin sodium and ammonium chloride was deemed necessary because of the hepatomegaly and mild ankle edema. On October 4, 1951, she was treated in the accident room for acute pulmonary edema following an altercation with a neighbor. She complained of vague pains in her fingers, ankles, and wrists and occasional feverishness at night. Acetylsalicylic acid (Aspirin) therapy was begun at that time, and she continued to take this drug on her own initiative almost continuously for the remainder of her life.

During 1952 the patient was on the whole much better subjectively and her heart was usually quieter on examination. The Graham Steell murmur was frequently inaudible, and the apical rumble was less prolonged and loud. There were no bouts of acute pulmonary edema and no illness requiring hospitalization. The ventricular rate was always rapid, however, and the dosage of digitalis leaf was increased to 0.2 gm. per day, at which level it was maintained for the rest of her life. It was during the year 1952 that steady rise in arterial blood pressure was noted.

Unlike the preceding year, 1953 was one of much difficulty for the patient. A Gatch bed was found necessary for maximum comfort at night. The liver became even larger, reaching to or below the iliac crest. Several of her relatives had infectious hepatitis at this time. The serum bilirubin was measured at 3.2 mg. per 100 cc., and there was 28% retention of sulfobromophthalein (Bromsulphalein) in 30 minutes, but alkaline phosphatase, total serum proteins, albumin-globulin ratio, thymol turbidity, and cephalin flocculation were not abnormal. White blood cell count and sedimentation rate were consistently at the upper limit of normal or slightly elevated. Repeat cardiac catheterization was attempted on April 28, 1953, but had to be abandoned because of the development of acute pulmonary edema. Small lesions suggestive of petechiae were seen several times. In the Fall of 1953 she complained frequently of feverishness, night-sweats, and vague joint pains. A series of blood cultures in November were negative, with exception of one from which Streptococcus faecalis was grown. In September, 1953, two admissions to the hospital were necessitated by the development of what was clearly a pulmonary embolus, to the left upper lobe on the first occasion and to the right lower lobe on the second. Throughout this period the physical signs of mitral stenosis were most impressive, as is indicated by the comment of one clinician who saw her for the first time: "Interestingly she sounds as though she would be an excellent candidate for valvulotomy except that she has had one."

By April, 1954, the liver had receded considerably in size and its edge was only about 1 fingerbreadth below the right costal margin. In August the sedimentation rate was 21 mm. At no time during her entire period of observation was the hematocrit level depressed.

The patient's last clinic visit was on Sept. 2, 1954. At that time she seemed better than usual and was for that reason instructed to return in three months.

The patient died in profound acute pulmonary edema in the early morning hours of Oct. 8, 1954. On the previous day she had done a large wash and walked some 10 blocks for shopping and other errands. She went to bed in her apartment, which was at that time occupied only by herself. It seems that she developed acute dyspnea and tried to attract the attention and assistance of her neighbors. There was considerable delay in getting assistance and in getting her to the hospital. On arrival at the hospital she was unconscious and cyanotic, and she died very shortly thereafter.

During the last two years of her life the patient's blood pressure was rather consistently about 180/120 mm. Hg, and urinalysis usually revealed mild albuminuria. Intravenous pyelograms performed on April 26, 1954, were interpreted as normal. At no time was there any episode suggesting acute renal infarction of major proportions, and no hematuria was ever observed. Of the some 70 visits to the hospital in the four and one-half years after operation, only once (April 27, 1950) was any reference made to backache.

The positive findings of the necropsy examination were mainly those in the heart, lungs, and kidneys. The lungs weighed 1360 gm. and were obviously boggy with slightly bloody edema fluid. The larger airways were filled with foamy blood-tinged material. The heart weighed 520 gm. Pericardial adhesions overlay the left auricular area. The left atrium was dilated, and its lining was diffusely opaque. No antemortem thrombi were present. Other than in the mitral valve, no valvular lesions were discovered. The pulmonary artery was dilated, and the pulmonary ring was enlarged. (The murmur

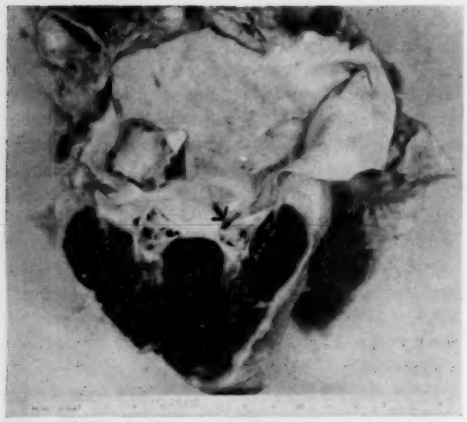
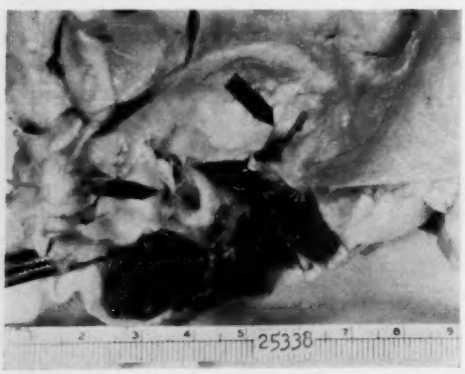


Fig. 1.—Dense scarring of the mitral curtain extending onto the chordae tendineae is demonstrated. The arrow indicates the area of the lateral commissurotomy scar, which is better demonstrated in Figure 2. (A section for histological examination has been removed from the wall of the atrium above the valve.)

interpreted as a Graham Steell sound was clearly due to that.) The mitral valve cusps were densely fibrosed, with thickening, deformity, and adhesion of the chordae tendinae. The orifice was narrowed to such an extent that it would not admit the tip of the small finger. In the area of each commissure (at the points where the tears had been produced at operation) a vascular linear scar was apparent. A moderate amount of calcification in the valve curtain was identified. The right and left kidney weighed 140 and 115 gm., respectively. Both were the site of typical cortical infarctions. The main renal arteries were normally patent, however. The brain was cut and examined by Dr. David B. Clark, who found no abnormality. Histologically, no definite evidence of rheumatic activity was discovered in the myocardium.

Fig. 2.—Shown on the right is the long vascular scar where lateral commissurotomy was performed. The arrow on the left indicates the other scarred area.



SUMMARY OF CASE

In this white woman, with signs and symptoms of clinically pure mitral stenosis, mitral valvulotomy was performed at the age of 31 years. At the time of operation there were evidences of rheumatic activity in the form of mild leucocytosis, slight temperature elevations, and elevated sedimentation rate. Following operation there were continuing suggestions of rheumatic activity. The initial improvement in auscultatory signs and clinical state was not maintained, and the patient died in acute pulmonary edema almost 57 months after operation. Autopsy revealed tight mitral stenosis. Scars of refusion at the sites of the seemingly adequate commissurotomy were evident. Renal infarction provided adequate explanation for the hypertension which the patient developed in the last two years of life.

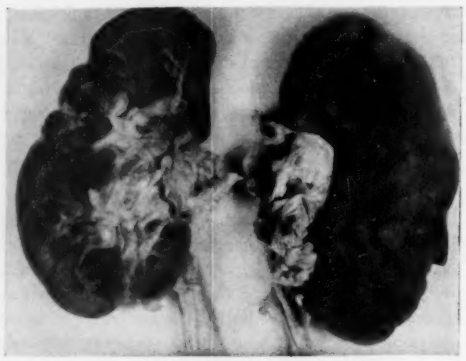


Fig. 3.—Scars of renal infarcts, which were probably responsible for hypertension in this patient.

COMMENT

In this case the evidence of rheumatic restenosis of the mitral valve is thoroughly convincing from both the clinical and the pathological standpoint. The evidence is also unmistakable that the rheumatic process was active at the time of mitral valvulotomy. At least low-grade activity was probably present continuously thereafter. If the experience accumulated since 1949 had been available at that time, mitral valvulotomy would not have been performed in the face

of these signs or, if necessary, would have been performed after treatment with cortisone.

Although other factors such as congestion and possibly hepatitis may have played a role in the hepatomegaly, it is possible that this impressive feature of the patient's clinical picture was in some way related to the active rheumatic process. Easy bruisability was also rather impressive, and petechia-like lesions were noteworthy. The latter, together with lesions of the nailbeds indistinguishable from splinter hemorrhages of subacute bacterial endocarditis, led frequently to suspicions of valvular infection. Two possible explanations for these lesions come to mind: (1) local rheumatic lesions of blood vessels and (2) small sterile emboli. The prothrombin time was never sufficiently prolonged to afford a basis for the finding. Whatever the correct explanation, we have observed these phenomena sufficiently often in rheumatic subjects to consider them by no means pathognomonic of bacterial endocarditis. Others of the patients have even had Roth spots of the retina. The one positive blood culture among many (in November, 1953) is noteworthy. It remains unexplained, inasmuch as no vegetations were discovered at autopsy, and it probably represents transient bacteremia from some unidentified focus of infection. Positive results are sometimes found in "normal" subjects when repeated cultures are made.* In another recent patient (A. DiU., 670396), in whom a high degree of rheumatic activity was discovered at autopsy, splinter hemorrhages and a positive blood culture for S. faecalis led to a mistaken diagnosis of subacute bacterial endocarditis.

It is of note that sulfonamide prophylaxis, although religiously pursued, did not prevent the clinical evidences of smoldering rheumatism and did not prevent the mitral restenosis. This prophylaxis was given for 10 months before operation and for essentially the entire postoperative period. The course of events is consonant with current impressions [7] that sulfonamide provides much less effective prophylaxis against streptococcal infection than does penicillin.

Renal embolism is obviously a possible basis for the hypertension which developed in this patient.[8] Probably the soil was prepared for the development of hypertension by the family background of hypertension and by the temperament of the patient, which, although not described in detail, was highly excitable. (The genetic and personality factors are, to be sure, not independent variables.) It is surprising that there were no definite acute clinical manifestations of renal infarction. Pain in the right side of the abdomen, particularly the right upper quadrant, was often striking but was always interpreted as hepatic in origin. The predominant localization of the infarctions to the right kidney may indicate that these pains arose, in part at least, from that organ.

One other patient, the second to be operated on at this hospital, required reoperation 38 months later. In that patient adequate relief of obstruction was not unequivocally provided at the first operation, although there did appear to be temporary clinical improvement. In retrospect, we believe that the patient described above should have had a repeat operation, possibly under cortisone therapy, and that she should have been given penicillin prophylaxis. When outspoken evidences of restenosis develop, the physician and surgeon must have the strength of their convictions and the humility of spirit to recommend reoperation to the patient.

SUMMARY AND CONCLUSIONS

A case of autopsy-confirmed rheumatic mitral restenosis is reported. Death from acute nocturnal pulmonary edema occurred 57 months after operation. Smoldering rheumatic activity at the time of valvulotomy and inadequacy of sulfonamide prophylaxis are considered to be leading factors in the restenosis.

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Parenteral Reserpine in Treatment of Hypertensive Emergencies

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The treatment of hypertensive emergencies usually requires a potent drug which will promptly reduce the blood pressure. The condition of the patient and the necessity for a rapid response usually make the oral route of drug administration inappropriate. As a result, the primary problems in therapy are those related to the parenteral route of drug administration and to the use of potent compounds which may produce an excessive reduction in blood pressure. These aspects have heretofore necessitated close supervision of the administration of these drugs. Veratrum alkaloids when administered intravenously are probably the most potent agents for reducing blood pressure in hypertensive patients. Their effect is as marked in the recumbent as in the upright position, a characteristic which makes them particularly suitable for the unconscious or bedfast patient. It is always possible to reduce a markedly elevated blood pressure within 10 to 20 minutes with an intravenous infusion of alkavervir (Veriloid).[1] However, the disadvantages to this route of administration are that constant supervision of the rate of infusion is required, excessive hypotension is quite possible, and the distressing side-effects of nausea and vomiting are not infrequent. The inconvenience of prolonged therapy of this nature has led to the use of veratrum alkaloids intramuscularly. The results have shown less consistent and reproducible blood pressure effect than after intravenous administration.* However, less nursing care is required.

The ganglion-blocking drugs, hexamethonium and pentolinium (pentapyrrolidin), are frequently used in the treatment of acute emergencies because of their potent hypotensive effect both orally and parenterally.† The chief disadvantage with these drugs lies in a primary orthostatic blood pressure effect. Therefore, it is not always possible to maintain a sufficiently lowered blood pressure in the supine position. When given parenterally, they must also be administered under close medical supervision, since excessive blood pressure reduction can occur.

Peripheral (adrenergic) blocking agents have received clinical trial but have been less effective than veratrum or ganglion-blocking drugs.‡ The blood pressure depression which occurs during their use, as with agents producing ganglionic blockade, is more marked in the upright position. The drugs in this group which have been available for clinical use have had the disadvantage of either insufficient potency to reduce the supine blood pressure consistently (phentolamine [Regitine]; Hydergine) or so great a potency that excessive hypotensive blood pressure levels are frequently observed (N-phenoxyisopropyl-N-benzyl-β-choroethylamine [Dibenzyline]; N, N-dibenzyl-β-chloroethylamine [Dibenamine]). The occurrence of an excessive hypotensive effect with a peripheral

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* References 2 and 3.

† References 4-6.

‡ References 7 and 8.

blocking drug such as Dibenzyline must be regarded with fear, since there are no vasopressor agents which will reverse such a response. The purpose of the present communication is to report results and observations on the use of reserpine by parenteral administration for the treatment of hypertensive emergencies. Preliminary observations indicated that intravenous administration of reserpine in doses of 1 to 3 mg. produced a significant decrease in blood pressure in 76% of 17 hypertensive patients, and normotensive levels were achieved in one-half of the patients.[9] Therefore, in the current report, the drug was subjected to further clinical trial, with the use of higher doses intravenously and intramuscularly.

METHODS AND MATERIALS

Reserpine § was given parenterally for periods varying from 1 to 17 days to three groups of hypertensive patients: (1) severe progressive hypertensive cardiovascular disease, (2) toxemia of pregnancy, and (3) acute glomerulonephritis. All the patients were hospitalized during the period of therapy. Blood pressure determinations were made every one-half to one hour during the first two days (or longer) of therapy, after which they were made every two to four hours for the remainder of the treatment period. Upright blood pressure determinations were obtained at intervals whenever the condition of the patient would permit. During the initial phase of the study, the intravenous route was utilized primarily, but as the study progressed the drug was given almost exclusively by the intramuscular route, except for occasional intravenous injections during the first day of therapy. The procedure for intravenous administration consisted of diluting the drug in 100 cc. of 5% dextrose and infusing over a period of 20 to 30 minutes. The drug was not diluted for intramuscular administration.

Group 1—Severe Progressive Hypertensive Cardiovascular Disease.—There were a total of 14 patients in this group, 10 with malignant hypertensive cardiovascular disease and 4 with severe benign hypertensive cardiovascular disease manifested by marked, persistent hypertension accompanied by one or more complications involving the cardiac, renal, or cerebral vascular region. The general procedure was to administer 2.5 or 5 mg. of reserpine initially, either intravenously or intramuscularly. In most cases a definite schedule was established after the first dose, derived on the basis of the degree and duration of blood pressure reduction. The interval and dose of reserpine were subsequently adjusted on the basis of the blood pressure recordings, in order to achieve the desired blood pressure level whenever possible. The dose requirement of reserpine varied between the extremes of 1 and 10 mg., and the interval, from 4 to 24 hours or longer. Therapy was gradually converted to the oral route as soon as it became feasible. Reserpine was the initial oral agent, and either pentolinium ‖ or hydralazine ¶ was added in the cases in which blood pressure control was not adequate with oral reserpine alone.

Group 2—Toxemia of Pregnancy.#—This group comprised a total of six patients, four with severe preeclampsia alone and two with hypertensive vascular disease and associated severe preeclampsia. The same general procedure for drug administration was followed as in the patients in Group 1. The initial dose was usually 2.5 or 5 mg., and subsequent dosage and frequency of administration were determined on the basis of the blood pressure response. The first injection was given intravenously, and subsequent injections were given by the intramuscular route. The patients received insignificant amounts of sedative drugs during the period of therapy. No other antihypertensive drugs were given in conjunction with the parenteral reserpine. Two patients in this group received reserpine during the immediate postpartum period, at which time marked blood pressure spikes occurred.

Group 3—Acute Glomerulonephritis.—Eight patients of pediatric age with acute glomerulonephritis were given reserpine parenterally. At the beginning of the study, the drug was administered intravenously in the amount of 25γ per kilogram of body weight. As the study proceeded, both the intravenous and intramuscular routes were used, and the dose was increased to 50 to 100γ per kilogram for the purpose of increasing the degree of blood pressure reduction. The frequency of drug administration was usually not oftener than once daily. The majority of the patients in this group received reserpine for only a brief period, since the hypertensive phase usually persisted for only a few days.

In addition to the above three groups of patients, there was one patient who developed a hypertensive crisis as a manifestation of an acute lower nephron nephrosis following a transfusion reaction and was given a single injection of 2.5 mg. of reserpine intramuscularly.

§ Furnished by Ciba Pharmaceutical Products, Inc., as Serpasil and by Riker Laboratories, Inc., as Serpiloid.

‖ Furnished by Wyeth Laboratories, Inc., as Ansolysen.

¶ Furnished by Ciba Pharmaceutical Products, Inc.

Treatment directed by Dr. Jack Moore, Department of Obstetrics.

RESULTS

The clinical status of each patient prior to receiving treatment with parenteral reserpine is summarized in Table 1. The blood pressure and clinical response to therapy are outlined in Table 2.

Group 1—Severe Progressive Hypertensive Cardiovascular Disease

The data in Table 1 relative to the 14 patients in this group are indicative of severe hypertensive disease, and the patients can be considered to present a "hypertensive emergency." Ten of the patients had clinical findings characteristic of the malignant phase (Cases 1 to 10), and 4 had findings compatible with a severe form of benign hypertensive cardiovascular disease (Cases 11 to 14). Of the 10 patients with malignant hypertension, there were 4 with severe and 1 with moderate renal insufficiency. The cerebral complications consisted of hypertensive encephalopathy in six patients, cerebral hemorrhage in one patient, and cerebral thrombosis in two patients. Seven of the patients with malignant hypertension exhibited manifestations of congestive heart failure. The clinical data in connection with the four patients with severe benign hypertensive cardiovascular disease reveal that each had one or more complications involving the cardiac, renal, or cerebral vascular region in conjunction with marked, persistent hypertension.

The blood pressure began to decrease slowly and insidiously in one to four hours after the parenteral administration of reserpine to patients in this group and attained a maximum decrease two to five hours after the administration. This latent period between injection of the drug and onset of effect and the slow, insidious decrease in blood pressure were the characteristic features of the blood pressure response to parenteral reserpine. The duration of reduction in blood pressure was variable in different patients, the extremes being 2 to 24 hours or longer. The average duration was eight hours. The period of reduced blood pressure after parenteral reserpine was, however, fairly consistent for each individual patient. Therefore, the amount of drug required and the frequency of administration could readily be individualized for each patient. The degree of depression in blood pressure did not appear to be remarkably different after administration by the intravenous or intramuscular routes. However, the onset of significant depression was frequently slower after intramuscular injections, and in some instances the duration was more prolonged after this route. There was a moderate orthostatic effect in the patients in whom upright blood pressure recordings were made, but this was observed only after considerable blood pressure reduction was present in the recumbent position, with the exception of one patient (Case 14, Table 2) in whom a marked orthostatic response occurred during three days of therapy with intramuscular reserpine. This patient had previously had a sympathectomy for severe hypertension but had derived no benefit from the standpoint of a reduction in blood pressure.

All the patients in this group obtained a significant blood pressure effect after parenteral reserpine (decrease in the mean blood pressure of 20 mm. Hg or more), and the maximal depression of blood pressure in the supine position was within the normotensive range in nine (64%) of the patients. After 2.5 or 5 mg. of reserpine was administered on a regular schedule every 4 to 12 hours, the blood pressure tended to stabilize over a period of two to three days to normotensive or moderately hypertensive levels. Excessive hypotension did not occur in the recumbent position; however, occasionally the systolic pressure was slightly below 100 mm. Hg in the standing position. In patients who could not be rendered normotensive with parenteral reserpine, the maximal antihypertensive effect was elicited with 5 mg. administered every four to six hours intramuscularly. Doses above this level at the same intervals did not significantly enhance the antihypertensive effect, but they were productive of more side-reactions. In some patients, particularly those with malignant hypertension without marked renal insufficiency, a decrease in the dose or frequency

TABLE 1.—*Clinical Status of the Patients Prior to Therapy with Parenteral Reserpine*

Patient	Age, Yr.	Race	Sex	Diagnosis*	Urinalysis†					Laboratory Observations				Complications					
											Electrocardiogram		Chest Roentgenogram			Cerebral			
					Sp. Gr.	Alb.	RBC	WBC	Casts	B. U. N. Mg./100 Cc.	LVH*	Non-specific Changes	Cardiac Enlargement	Renal‡	Cardiac, Heart Failure§	None	Enceph.*	Thrombosis or Hemorrhage	Fundi‖
Group 1.—Severe progressive hypertensive cardiovascular disease																			
1. B. J.	27	N	F	MHCVD	1.020	2+	0	0	0	9	1	..	0	1+	0	1	..	..	4+
2. W. M. W.	42	N	F	MHCVD	1.022	3+	0	0	0	12	1	..	Mod.	1+	0	..	1	1	4+
3. D. C.	48	W	M	MHCVD	1.010	0	Few	0	Few	34	..	1	Mod.	2+	0	..	1	..	4+
4. W. M. W.	35	N	F	MHCVD	1.029	0	10	5	0	14	1	..	Mod.	1+	1+	..	..	1	4+
5. G. L. M.	41	W	F	MHCVD Le Riche syndrome	1.011	4+	Many	0	Few	55¶	1	..	0	3+	3+	..	1	..	4+
6. C. C.	41	N	F	MHCVD	1.029	4+	Many	Few	0	21	1	..	Mod.	1+	3+	..	1	..	4+
7. A. S.	25	N	M	MHCVD	1.011	4+	30	15	Many	65	1	..	Marked	4+	4+	..	..	1	4+
8. H. H.	43	N	F	MHCVD	1.007	3+	10	Many	0	140	1	..	Marked	4+	3+	1	..	..	4+
9. A. D.	32	N	F	MHCVD	1.010	0	Many	0	0	90	..	1	Marked	4+	3+	..	1	..	4+
10. C. H.	49	N	F	MHCVD	1.012	3+	Many	Few	0	84	1	..	Mod.	4+	1+	..	1	..	4+
11. R. L.	51	N	M	Severe HCVD	1.005	Tr.	0	0	Few	50	1	..	Marked	2+	4+	..	..	1	3+
12. A. M.	59	N	M	Severe HCVD	1.015	Tr.	0	Many	0	66	1	..	0	3+	0	..	..	..	2+
13. J. W.	48	N	M	Severe HCVD	1,018	2+	0	Few	Few	75	1	..	Mod.	3+	2+	..	1	Subarachnoid hemorrhage	4+
14. W. B.	53	W	M	Severe HCVD	1.021	2+	0	10	0	36	1	..	Mod.	2+	0	..	..	1	2+
Group 2.—Toxemia of pregnancy																			
15. I. B.	24	N	F	SPE	1,020	2+	0	0	0	17	Normal‡	..	Not obtained	1+	0	1	..	..	1+
16. R. M. W.	34	N	F	SPE	1.010	2+	0	0	0	12	1	..	0	1+	0	1	..	..	1+
17. M. S.	26	N	F	SPE	1.007	Tr.	0	0	0	13	1	..	0	1+	0	1	..	..	1+
18. O. B. T.	34	N	F	SPE	1.025	1+	0	0	0	..	1	..	0	1+	0	1	..	..	1+
19. D. B.	34	N	F	HVD&SPE	1.005	3+	0	Few	0	6	1	..	Mod.	1+	0	1	..	..	2+
20. M. F. R.	22	N	F	HVD&SPE	1.015	0	0	0	0	10	1	..	Mod.	0	0	1	..	..	2+
Group 3.—Acute glomerulonephritis																			
21. O. H.	6	N	M	AGN	1.022	4+	10	Many	Few	5	1	..	0	1+	0	..	1	..	Normal
22. D. W.	3	N	F	AGN	1.030	Tr.	0	0	0	6	1	..	0	1+	Mild	1	..	..	Normal
23. P. S.	7	W	M	AGN	1.020	3+	60	Many	0	42	..	†QT interval	0	2+	0	..	1	..	Normal
24. G. B.	3	N	M	AGN	1.022	2+	30	15	Few	35	..	1	.....	2+	Marked	1	..	..	Normal
25. J. P.	6	W	F	AGN	1.015	4+	Many	Many	Many	122	1	..	0	3+	0	1	..	..	Normal
26. G. M.	4	N	M	AGN	1.015	1+	25	15	Few	12	1	..	Mod.	1+	Mod.	..	1	..	Normal
27. B. C.	6	N	M	AGN	1.015	2+	0	Many	0	19	1	..	Mod.	1+	Mod.	1	..	..	Normal
28. C. S.	5	N	F	AGN	1.015	4+	Many	10	Many	26	..	†PR interval	Mod.	2+	Mild	1	..	..	Normal

* MHCVD, malignant hypertensive cardiovascular disease; HCVD, hypertensive cardiovascular disease; HVD, hypertensive vascular disease; SPE, severe preeclampsia; AGN, acute glomerulonephritis; LVH, left ventricular hypertrophy; Enceph., encephalopathy.

† Alb., albumin; Tr., trace; Sp. Gr., specific gravity.

‡ Renal impairment was graded on the following basis: 1+, abnormal urinalysis or renal function tests without azotemia; 2+, mild azotemia (blood urea nitrogen between 20 and 50 mg./100 cc.); 3+, moderate to severe azotemia (blood urea nitrogen above 50 mg./100 cc.); 4+, uremia.

§ Functional capacity graded from I to IV, according to the classification of the American Heart Association.

‖ Keith-Wagener-Barker classification.

¶ The elevated B. U. N. in this patient was primarily due to dehydration, since it returned to normal after fluid and electrolyte administration.

‡ Cases 15-28 had normal electrocardiograms unless otherwise indicated.

TABLE 2.—*Summary of Blood Pressure and Clinical Response in the Patients Treated with Parenteral Reserpine*

Patient	Maximal* Effective Dose, Mg.	Minimal† Effective Dose, Mg.	Control B. P., Supine	B. P. at Maximum Response, Supine	Blood Pressure Reduction: Onset,‡ Hr.	Blood Pressure Reduction: Duration,§ Hr.	Interval Between Injections, Hr.	Pulse Rate‖: C	Pulse Rate‖: D_1	Duration of Therapy, Days	Clinical Outcome
Group 1.—Severe progressive hypertensive cardiovascular disease											
1. B. J.	4	3	220/150	120/70	2-4	4-12	12 (i.m. or i.v.)	88	70	15	Marked improvement; converted to oral reserpine and pentolinium
2. W. W.	4	1	245/160	100/60	2-3	12-24	12-24 (i.m. or i.v.)	90	65	9	Marked improvement; converted to oral reserpine and pentolinium
3. D. C.	3	2	260/136	180/98	4	4-8	4-8 (i.v.)	90	64	8	Moderate improvement; converted to oral reserpine and hexamethonium
4. W. M. W.	5	2.5	290/150	120/80	3	8-12	8-12 (i.m.)	100	85	14	Marked improvement; converted to oral reserpine and pentolinium
5. G. L. M.	5	2.5	230/160	140/80	1 (i.v.) & 3 (i.m.)	16 initially, then 4-8	4-8 (i.m.)	88	50	17	Marked improvement; converted to oral reserpine and pentolinium
6. C. C.	5	2.5	280/190	140/85	3	12	12 (i.m.)	100	96	15	Marked improvement; converted to oral reserpine and pentolinium
7. A. S.	10	5	250/190	200/130	2-3	4	8 (i.m. or i.v.)	96	70	7	Death from uremia and cerebral hemorrhage
8. H. H.	3	1.5	210/140	140/100	2	4-6	24 (i.v.)	90	85	3	Death from uremia
9. A. D.	2	..	300/180	130/80	3	18 initially, then 4	4-12 (i.v.)	94	90	3	Death from uremia
10. C. H.	5	5	240/150	210/110	3	4-6	6 (i.m.)	70	82	7	Uremia became more marked
11. R. L.	5	5	260/170	170/100	3-4	8	8 (i.m.)	116	70	13	Marked improvement; converted to oral reserpine and pentolinium
12. A. M.	2.5	2.5	205/135	140/100	3-4	8	8 (i.m.)	104	72	6	Azotemia increased; converted to oral reserpine and hydralazine
13. J. W.	4	3	230/150	130/80	3	8	8 (i.m.)	90	70	9	Cerebral status improved; converted to oral reserpine and hydralazine
14. W. B.	5	5	240/160	140/110	3-4	2-3	4-6 (i.m.)	60¶	56	3	Clinical status unchanged; converted to oral reserpine and pentolinium
Group 2.—Toxemia of pregnancy											
15. I. B.	10	..	185/135	100/70	1	Remained normotensive	Given 1 time (i.v.)	72	62	1	Recovered; uneventful delivery of a normal infant
16. R. M. W.	5	2.5	190/125	130/70	4	12-24	8-24 (i. m.)	100	84	7	Recovered; uneventful delivery of a normal infant
17. M. S.	5	2.5	180/120	120/70	1-2	12	12-24 (i.m.)	48#	60	3	Recovered; uneventful delivery of a normal infant
18. O. B. T.	5	2.5	180/110	110/80	2	12	8-24 (i.m. or i.v.)	80	75	5	Recovered; uneventful delivery of a normal infant
19. D. B.	3	..	240/150	150/100	3	12	Single inj. (i.v.)	90	80	1	Improved; converted to oral Rauwolfia
20. M. F. R.	5	2.5	200/130	130/80	2	12	12 (i.m.)	84	60	5	Improved; converted to oral reserpine
Group 3.—Acute glomerulonephritis											
21. O. H.	1	0.5	175/120	125/80	1-2½	14-18	24 (i.v.)	54	54	4	Recovered
22. D. W.	0.5	0.25	170/125	110/70	½-1½	3-6	24 (i.v.)	100	100	2	Recovered
23. P. S.	1	..	180/130	150/120	3	3	Single inj. (i.v.)	80	72	1	Recovered
24. G. B.	0.5	..	155/105	120/70	1 (i.v.) & 3 (i.m.)	5 (i.v.) & 16 (i.m.)	24 (i.v. or i.m.)	42	42	2	Death from congestive heart failure
25. J. P.	3	..	150/90	120/80	2½	18	Single inj. (i.v.)	80	80	1	Progressed to subacute stage
26. G. M.	2	..	160/138	120/80	1½	18	24 (i.m.)	100	90	2	Recovered
27. B. C.	2	..	140/100	110/70	2	Remained normotensive	Single inj. (i.m.)	92	90	1	Recovered
28. C. S.	2.5	..	180/130	115/70	5	16	Inj. repeated after 5 hr. (i.m.)	110	80	1	Recovered

* Maximal effective dose used during the period of therapy.
† Minimal effective dose used during the period of therapy; usually followed prolonged drug therapy.
‡ Onset of significant blood pressure reduction.
§ Duration of significant blood pressure reduction.
‖ C, control pulse rate; D_1, pulse rate during therapy with parenteral reserpine.
¶ This patient was receiving oral Rauwolfia prior to therapy with parenteral reserpine.
# This patient was receiving oral reserpine prior to therapy with parenteral reserpine.

of administration of reserpine could be effected after several days of therapy on a regular schedule. Occasionally, the blood pressure was controlled on oral reserpine alone for several days or even as long as a month after parenteral reserpine was discontinued, indicating that the drug is either slowly excreted or detoxified. The patients with marked renal impairment were the most resistant from the standpoint of obtaining and maintaining a significant blood pressure response. These patients were only treated for brief periods for the purpose of relieving associated acute complications, such as hypertensive encephalopathy, or for the purpose of observing the antihypertensive potency of parenteral reserpine in this type of circumstance.

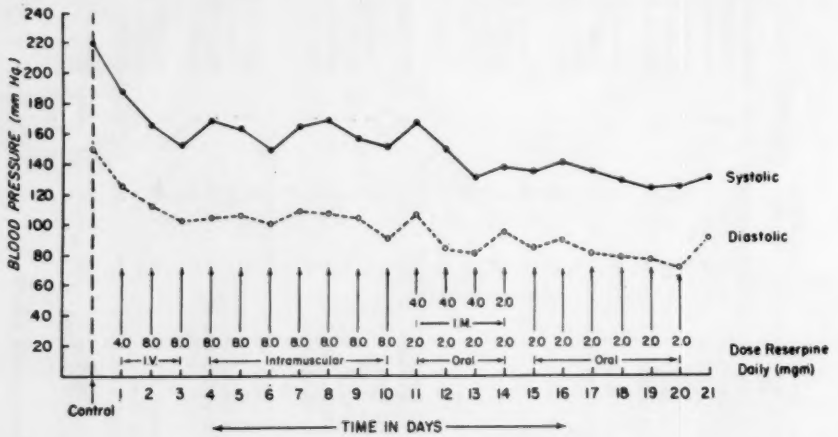

Fig. 1.—A patient with malignant hypertension. The blood pressure was reduced to mildly hypertensive or normotensive levels during three weeks of therapy with reserpine. The drug was administered parenterally every 12 hours for 10 days, at which time it was started orally and parenteral administration was slowly discontinued. The blood pressure was adequately regulated with oral reserpine alone for one month (see Case 1).

The beneficial effects of therapy in this group of patients were reflected in the disappearance of papilledema in 7 of 11 patients with this physical finding and the relief of hypertensive encephalopathic manifestations in 4 of 6 patients. The two patients in whom hypertensive encephalopathy was not relieved had associated uremia. The encephalopathy associated with a subarachnoid hemorrhage in one patient appeared to be improved by blood pressure depression with parenteral reserpine. An electrocardiographic pattern of myocardial ischemia disappeared in one of the patients during treatment, and marked congestive heart failure appeared to be benefited by sustained blood pressure reduction in another. An analysis of the clinical outcome for the group shows that six of the patients with malignant hypertension have recovered from the malignant phase and the condition is now well regulated on oral therapy; three died as a result of uremia, and one has severe uremia at the present time. All the patients with severe benign hypertensive cardiovascular disease are alive and are maintained on oral antihypertensive therapy.

Case 1 (Tables 1 and 2).—B. J., a 27-year-old Negro woman, was admitted to the hospital with a history of severe frontal headaches for four to five years and progressive blurring and diminution of vision for the past two months. She noted that she could read only the largest print at the time of admission. The patient denied any previous knowledge of hypertension, and no history of known renal disease or urinary symptoms could be elicited. There was no history suggestive of cardiovascular complications. Physical examination revealed a blood pressure of 220/150 and a pulse rate of 88 beats per minute. The patient generally appeared in a good state of nutrition and was in no evident acute distress. The fundi revealed bilateral

papilledema and many fresh hemorrhages and exudates. The lungs were clear to percussion and auscultation. There was no evidence of congestive heart failure, although the heart was slightly enlarged. The rhythm was regular and no murmurs were audible. The laboratory findings (Table 1) consisted of a normal urinalysis with the exception of mild albuminuria. The blood urea nitrogen was 9 mg. per 100 cc. The electrocardiogram showed left ventricular hypertrophy and diffuse myocardial ischemia. The clinical impression was malignant hypertensive cardiovascular disease. On the day of admission, parenteral reserpine was started. The period of therapy is shown graphically in Figure 1. Reserpine was administered intravenously for the first three days, after which the intramuscular route was used for seven days. The dose throughout this time was 4 mg. every 12 hours. On the 11th day of hospitalization, oral therapy was initiated with reserpine. At the same time the intramuscular reserpine was decreased to 2 mg. every 12 hours for three days, then 2 mg. daily for one day, and then parenteral therapy was discontinued on the 15th hospital day. The blood pressure values plotted in Figure 1 represent the average of blood pressure recordings during each day of hospitalization. The

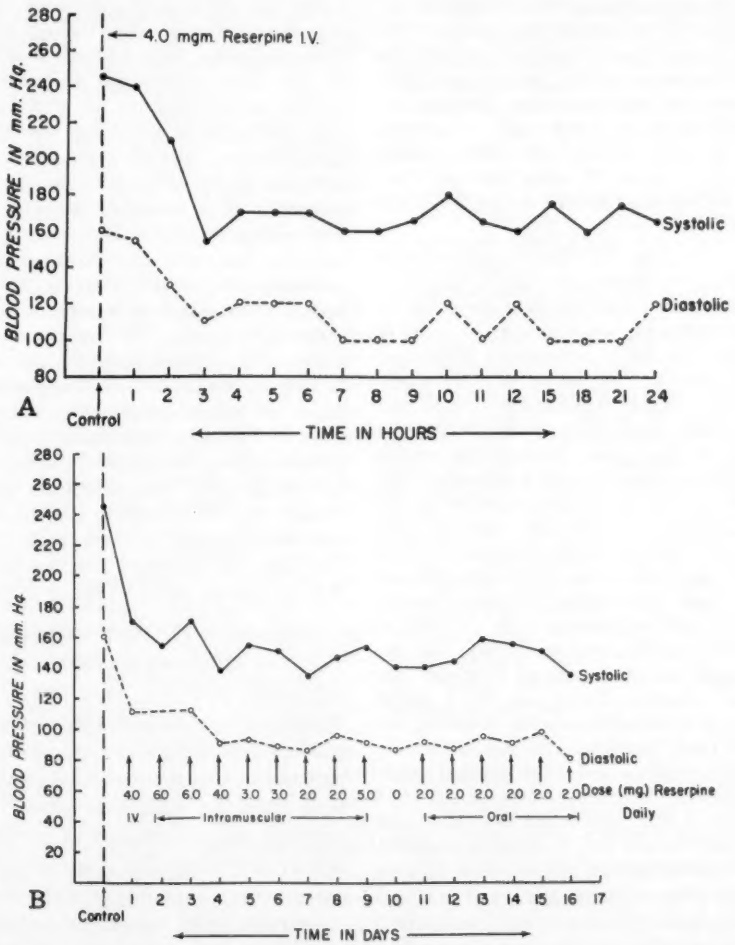

Fig. 2.—*A*, a patient with malignant hypertension. The blood pressure response to 4 mg. of reserpine administered intravenously. The onset of significant blood pressure reduction occurred two hours after the injection, and maximum reduction occurred at three hours. Significant blood pressure effect was still present after 24 hours. *B*, the blood pressure response during therapy with parenteral reserpine and for one week after conversion to the oral route. The blood pressure was maintained quite consistently at normotensive or mildly hypertensive levels. One week following discontinuation of parenteral reserpine, pentolinium was added because of a gradual loss of adequate reduction in blood pressure.

recordings were in the mildly hypertensive range during the first 13 days of therapy, after which they were persistently normotensive until the time of hospital discharge, three weeks after admission. The last week of therapy in the hospital consisted of oral reserpine alone. The blood pressure remained well controlled with oral reserpine alone until one month after discontinuation of parenteral reserpine, at which time the blood pressure began to rise again. Pentolinium was added at that point, and the hypertension has been well controlled. Symptomatically, the headaches disappeared during the first two days of therapy, and the patient's vision progressively improved during the period of hospitalization. Papilledema slowly disappeared, as did the retinal hemorrhages. The side-effects during therapy consisted primarily of considerable somnolence during the first week, after which it decreased noticeably with continued reserpine administration. There was a moderate bradycrotic effect, the average pulse rate decreasing from a control of 88 to 70 during therapy. Conjunctival injection was observed during the initial few days of therapy only.

CASE 2 (Tables 1 and 2).—W. W., a 42-year-old Negro woman, was hospitalized with a history of onset of continuous occipital headache one day prior to admission, following which progressive lethargy appeared. On the day of admission a generalized convulsion occurred. Five months prior to admission the patient had been hospitalized for a subarachnoid hemorrhage, during which time she was unconscious for five days. Marked hypertension was noted at that time. She had progressively improved and was discharged after a period of two weeks, but she did not return for outpatient care. There was no history of known hypertension prior to the first hospital admission. No history of known renal disease could be obtained. Physical examination revealed the blood pressure to be 245/160 and the pulse rate to be 104 beats per minute. The patient generally appeared lethargic, but she was rational and oriented. There was slight nuchal rigidity, but no remarkable neck vein distention was noted. The fundi revealed recent and old hemorrhages, with exudates and mild bilateral papilledema. The lungs were clear. On examination of the heart, the P. M. I. was in the sixth intercostal space and was localized and thrusting in character. There was a sinus rhythm, and no murmurs were audible. The liver was not palpable, and there was no peripheral edema. There was slight weakness of the left arm and leg, a residual of the previous cerebral vascular episode. The laboratory findings (Table 1) consisted of mild albuminuria, blood urea nitrogen of 12 mg. per 100 cc., moderate left ventricular enlargement on chest roentgenogram, and left ventricular hypertrophy on electrocardiogram. Lumbar puncture revealed a spinal fluid pressure of 360 mm. water. The spinal fluid was grossly clear, with normal cell count, 43 mg. per 100 cc. protein, and negative serology. The clinical impression was early malignant hypertensive cardiovascular disease. Treatment consisted of parenteral reserpine for a period of nine days, after which the drug was administered orally. An initial dose of 4 mg. was given intravenously, and the remaining parenteral therapy was by the intramuscular route. The blood pressure response to the initial dose of reserpine is plotted graphically in Figure 2*A*. The onset of significant blood pressure reduction was 2 hours after the injection was given; the maximal reduction appeared at 3 hours, and significant reduction was still present at 24 hours. The average daily blood pressure values throughout the period of hospitalization are graphically shown in Figure 2*B*. The blood pressure was maintained quite consistently at normotensive or mildly hypertensive levels with doses of 1 to 4 mg. administered every 12 to 24 hours. After parenteral reserpine was discontinued, on the 10th hospital day, the blood pressure continued at essentially the same levels for 1 week with oral reserpine alone, but satisfactory control was then lost. Pentolinium was, therefore, combined with the oral reserpine, which provided blood pressure regulation at normotensive or mildly hypertensive levels. The hypertensive encephalopathy rapidly cleared following the initiation of therapy, and the papilledema disappeared during the period of hospitalization. The side-effects consisted of somnolence, bradycardia, mild nasal congestion, conjunctival injection, burning of the eyes, and photophobia. The somnolence gradually decreased in intensity, and the conjunctival injection disappeared during the first week of treatment. The pulse rate decreased from a control value of 90 to an average rate of 65 during therapy.

Comment.—The two foregoing cases are examples of the effectiveness of short-term parenteral reserpine treatment of malignant hypertensive cardiovascular disease without marked renal insufficiency. There were six patients of this type, and all of them recovered from the malignant phase. The blood pressure was maintained at or near normotensive levels without constant or unusually close medical supervision of the therapy. The conversion from parenteral to oral therapy was accomplished without a marked increase in blood pressure, since the antihypertensive effect was lost slowly after discontinuation of parenteral reserpine. This allowed time for a slow titration of an effective and more potent oral agent.

CASE 11 (Tables 1 and 2).—R. L., a 52-year-old Negro man, was admitted to the hospital with an eight-year history of known hypertension. Three years prior to admission he developed exertional dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. He was, therefore, placed on a low-salt diet, digitalis, and mercurial diuretics. After this he returned irregularly to the cardiac clinic for the treatment of severe hypertension and associated congestive heart failure but could never be controlled adequately because of his failure to cooperate sufficiently with the therapeutic program advised. He had received veratrum and also combined reserpine and hexmethonium orally. Three weeks prior to admission dyspnea and orthopnea became progressively more marked, and peripheral edema rapidly increased. Pertinent physical findings at the time of admission consisted of a blood pressure of 260/170 and a pulse rate of 116 beats per minute. He appeared acutely and chronically ill, with severe dyspnea and orthopnea. The fundi showed Grade III changes. The neck veins were markedly distended. There were moist rales at both lung bases. The heart was enlarged to the left and downward. There was a sinus tachycardia, with a heart rate of 116, and no murmurs were audible. A diastolic gallop rhythm could be heard over the apical area. The liver was palpable 6 cm. below the right costal margin and was tender. Marked peripheral edema was present. The laboratory findings are summarized in Table 1 and revealed an abnormal urinalysis, showing a trace of albumin and occasional granular cast, and blood urea nitrogen of 50 mg. per 100 cc. Left ventricular hypertrophy was evident on the electrocardiogram, and marked left ventricular enlargement, on the chest roentgenogram. The clinical impression was severe benign hypertensive cardiovascular disease with marked congestive heart failure and moderate renal insufficiency. Therapy for the congestive heart failure consisted of bed rest, low-salt diet, digitalis, and oral diuretics (chlormerodrin [Neohydrin] and 2-acetylamino-1,3,4,-thiadiazole-5-sulfonamide [Diamox]). At the time of admission, the patient was given 5 mg. of reserpine intramuscularly, and this dose was repeated every 12 hours for 7 days and then every 8 hours for the next 2 days. Oral reserpine was then added, in a dose of 0.5 mg. four times daily. The intramuscular reserpine was slowly decreased and finally discontinued 15 days after admission. The average daily level of blood pressure during the period of therapy is graphically represented in Figure 3. The systolic pressure varied between 170 and 220 mm. Hg, and the diastolic pressure, between 90 and 120. A greater reduction in blood pressure did not seem feasible in view of the azotemia. Subsequent to hospital discharge, pentolinium was added to provide effective blood pressure control,

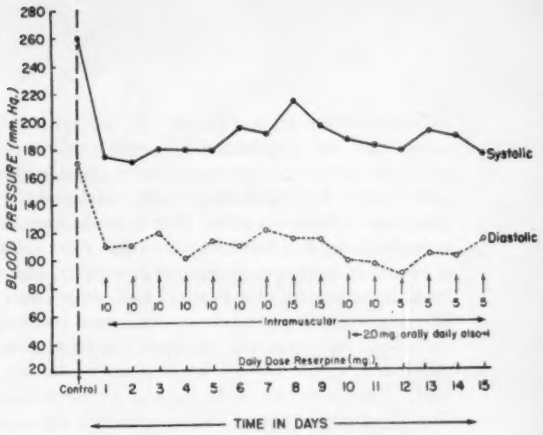

Fig. 3.—A patient with severe benign hypertensive cardiovascular disease with marked congestive heart failure and moderate renal insufficiency. The blood pressure effect during 15 days of treatment with intramuscular reserpine consisted of systolic pressure values ranging between 170 and 220 mm. Hg and diastolic pressure values between 90 and 120 mm. Hg. Treatment was not further intensified because of the renal impairment.

since oral reserpine alone was sufficiently effective for only a few days. The hospital course in addition to that which pertained to the blood pressure was featured by a prompt improvement in the congestive heart failure. The edema completely disappeared by the 10th hospital day, allowing discontinuation of the diuretics. The azotemia improved concommitantly with the improvement in cardiac status. The blood urea nitrogen was 36 mg. per 100 cc. at the time of discharge. Somnolence and weakness were prominent side-effects to the parenteral reserpine but decreased with continuous therapy. The pulse rate decreased from 116 on admission to 70 during treatment. Conjunctival injection was observed only during the initial few days of therapy. Mild muscle tremors occurred, and on the third day of treatment several frank chills were experienced. Moderate fever was recorded during that day only. The etiology of the chills and fever was not determined. However, the possibility of their being side-reactions to the reserpine was considered.

Comment.—Congestive heart failure did not prevent blood pressure responsiveness to parenteral reserpine, but normotensive levels were more difficult to obtain in the patients in whom this complication was present. In the above case, the azotemia improved concommitantly with the disappearance of congestive heart failure, indicating that the latter was a contributing factor to the renal impairment. Blood pressure reduction with reserpine probably contributed to the rapid improvement in cardiac status; however, this cannot be unequivocally stated.

Case 14 (Tables 1 and 2).—W. B., a 53-year-old white man, was hospitalized as a result of a foot infection and during the period of hospitalization was treated for three days with intramuscular reserpine. History revealed that a thoracolumbar sympathectomy had been performed five years prior to admission for severe hypertension, without benefit from the standpoint of a decrease in blood pressure. One and one-half years before admission a cerebral thrombosis had occurred, but there was no residual impairment at the time of examination in the hospital. There were no cardiovascular complications. The blood urea nitrogen had been slightly elevated for several months. The clinical impression was severe benign hypertensive cardiovascular disease with mild renal impairment and an old cerebral thrombosis. The therapeutic regimen prior to admission consisted of a combination of Rauwolfia and pentolinium administered orally. He was receiving large doses of pentolinium (200 mg. four times daily), and, irrespective of this, high blood pressure spikes were prone to occur. The oral pentolinium and Rauwolfia were discontinued 12 hours prior to initiation of parenteral reserpine. He was then given 5 mg. intramuscularly every six hours for one day and 5 mg. every four hours for the next two days. The recumbent blood pressure recordings after the initial injection are shown in Figure 4 and, following these, the average daily blood pressure value during the three days of treatment. The effect on blood pressure was not dramatic; however, a significant reduction occurred for about two hours after each injection. A rather marked orthostatic blood pressure effect was observed during the three days of treatment. Normotensive levels could not be attained except for a few determinations in the upright position. Intramuscular reserpine was discontinued after three days, and oral Rauwolfia and pentolinium were again started, which proved to be effective.

Comment.—The marked orthostatic effect was a feature of the above case. This could not have been due to the previously administered pentolinium, since the control blood pressure at the time of initiation of intramuscular reserpine was uniformly elevated in the recumbent and upright positions. The blood pressure could not be converted to a stable level in the normotensive range with 5 mg. of reserpine every four hours in this case. The patient responded to parenteral reserpine despite a failure to respond to Rauwolfia administered orally.

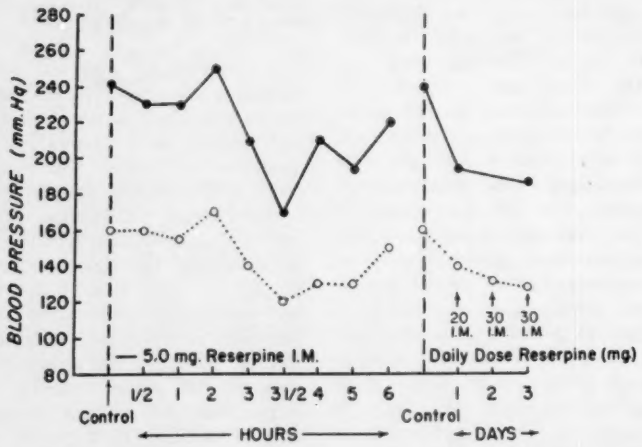

Fig. 4.—A patient with severe benign hypertensive cardiovascular disease with mild renal impairment and a previous cerebral thrombosis. This represents a patient who was quite resistant to parenteral reserpine. The drug was administered intramuscularly in doses of 5 mg. every four to six hours for three days. A significant reduction in blood pressure was observed for only about two hours after each injection, and normotensive levels could not be attained.

Group 2—Toxemia of Pregnancy

The six patients in this group received therapy with parenteral reserpine for periods varying from one to seven days. The clinical findings were consistent with a diagnosis of severe preeclampsia in four patients and benign hypertensive vascular disease with associated severe preeclampsia in two patients (Table 1). There were no remarkable vascular complications in any of the patients.

The blood pressure response to parenteral reserpine in this group was not remarkably different from that noted in the group with severe progressive hypertensive cardiovascular disease. The results of therapy as outlined in Table 2 show that all the patients obtained a significant blood pressure effect. The maximal reduction in pressure was in the normotensive range in all six patients. The dose of reserpine which was used varied from 2.5 to 10 mg.; however, the maximal effective dose was usually 5 mg. The interval of administration varied from 8 to 24 hours. Two of the patients received treatment during the immediate postpartum period, because of the development of marked blood pressure spikes at that time. Both of these patients had benign hypertensive vascular disease and associated severe preeclampsia. All of the patients in this group recovered uneventfully. There were no fetal complications.

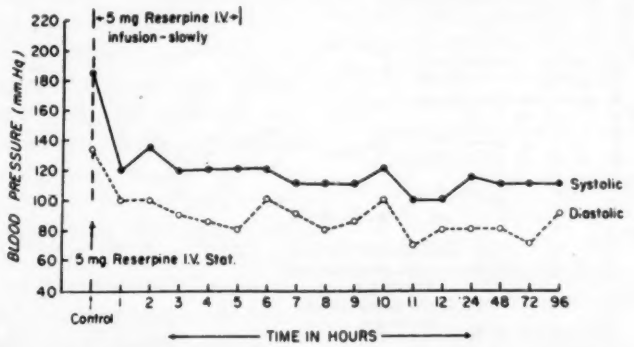

Fig. 5.—A patient with severe preeclampsia. This patient did not respond to bed rest and sedation. Five milligrams of reserpine was given intravenously, and this was followed by a slow intravenous infusion containing 5 mg. The blood pressure decreased to normotensive levels one hour after the initial injection and remained normotensive.

Case 15 (Tables 1 and 2).—I. B., a 24-year-old Negro woman, was admitted to the hospital during the eighth month of pregnancy, with a history of headaches, vertigo, and scotomata for one month previous to admission. Swelling of the feet, hands and face appeared two weeks before admission. There was no history of previous hypertension or toxemia of pregnancy. Physical examination revealed an initial blood pressure of 160/100 and a pulse rate of 64 beats per minute. The patient generally did not appear acutely ill. The fundi revealed only arteriolar spasm. There were no remarkable abnormalities on examination of the heart and lungs. Peripheral edema was present to the extent of 2+. Laboratory findings were not remarkable with the exception of 2+ albuminuria. The clinical diagnosis was severe preeclampsia. Upon admission the treatment consisted of bed rest, low-sodium diet, sedation, and diuretics. The blood pressure continued to increase, and seven hours after admission it was 185/135. At that time 5 mg. of reserpine was given intravenously over a period of 20 minutes. This was followed by a slow intravenous infusion containing 5 mg. of reserpine which was administered over a period of five hours. The antihypertensive effect is illustrated graphically in Figure 5. One hour after the initial injection, the blood pressure dropped to normotensive levels, and it remained so until the time of discharge, four days later. The patient became lethargic and slept most of the time during the day following reserpine administration but could be easily aroused. On the day following admission a normal infant was delivered.

Comment.—It is evident that the blood pressure depression which was observed in the above-described case of severe preeclampsia was a direct consequence of intravenous reserpine in that the condition was not responding to the use of bed rest and sedation alone.

Group 3—Acute Glomerulonephritis

The clinical findings in the eight pediatric patients with acute glomerulonephritis before treatment (Table 1) show that all the patients had albuminuria; six had either gross or microscopic hematuria; four had elevation of blood urea nitrogen; three had cardiac enlargement, and three had abnormal electrocardiograms. From the standpoint of

complications, five patients manifested congestive heart failure and three patients manifested hypertensive encephalopathy.

The characteristics of blood pressure response to parenterally administered reserpine were remarkably similar to those observed in the preceding two groups of hypertensive patients. The onset of blood pressure reduction occurred one-half to five hours after the drug was given, being one to two hours slower after the intramuscular than after the intravenous route. The duration of reduction varied from 3 to 18 hours or longer, and, in some cases, it was more prolonged after intramuscular than after intravenous injections. The dose during the initial phase of the study was 25γ per kilogram of body weight, but later in the study it was increased to 50 to 100γ per kilogram for the purpose of increasing the degree of blood pressure reduction. The drug was not given on a regular schedule but rather by injections after the blood pressure had returned to hypertensive levels. This procedure was followed in order to study the characteristics of blood pressure response, since the hypertensive phase in acute glomerulonephritis is quite variable in duration. Generally it did not appear necessary to give the drug at intervals more frequent than once daily.

Seven of the eight patients obtained a significant blood pressure effect after parenteral reserpine, and in six patients the normotensive level was attained. Six of the patients recovered; one patient progressed to a subacute stage, and one patient died as a result of congestive heart failure. Hypertension was not the primary factor in the progressive nature of the congestive heart failure in the latter case, since the blood pressure had been maintained at only slightly elevated levels.

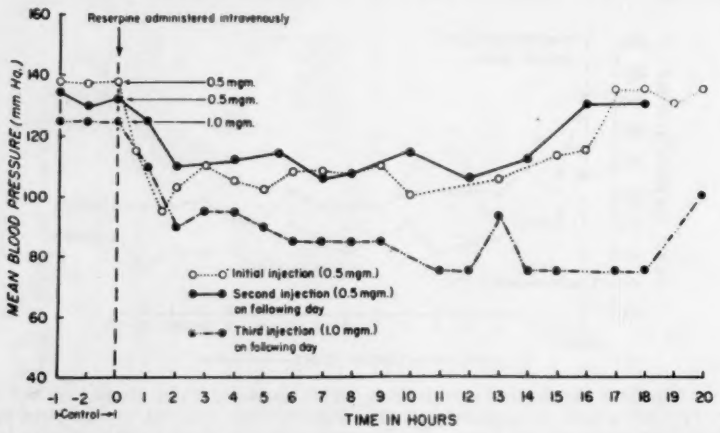

Fig. 6.—A patient with acute glomerulonephritis. The mean blood pressure response to three intravenous injections of reserpine is shown. Hypertensive levels were present at the time of each injection. The same characteristics of blood pressure response occurred after each injection, indicating that reserpine was responsible for the blood pressure depression.

Case 21 (Tables 1 and 2).—O. H., a 6-year-old Negro boy, was hospitalized with a history of frontal headache of five days' duration, edema of the extremities and periorbital area of four days' duration, and dark, red urine of four days' duration. There was no definite history of an antecedent upper respiratory infection. Physical examination showed a blood pressure of 175/120 and a pulse rate of 60 beats per minute. The child generally appeared listless. The lungs were clear. The heart appeared slightly enlarged on percussion. A sinus rhythm was present, and there were no murmurs heard. No edema was noted. The laboratory findings (Table 1) consisted of a urinalysis showing 4+ albuminuria, many red blood cells, 10 to 12 pus cells per high-power field, and a few granular casts. The blood urea nitrogen was 5 mg per 100 cc., and a chest roentgenogram and electrocardiogram were normal. The clinical diagnosis was acute glomerulonephritis. Reserpine was given on four occasions intravenously at daily intervals. The doses used were 0.5 and 1 mg. The antihypertensive effect fol-

lowing three of the injections is shown in Figure 6. The characteristics of this effect were essentially the same for each injection, consisting of the appearance of significant blood pressure reduction at 1 to 2 hours, persistence of reduction for 12 to 18 hours, and then a slow rise again toward preinjection levels. The only observed side-effect was lethargy. On the seventh hospital day, the hypertensive phase subsided. The urinalysis returned to normal before discharge from the hospital, 15 days after admission.

Comment.—The foregoing case is a conclusive demonstration that reserpine was responsible for the blood pressure depression which was observed, since the same characteristics of blood pressure response occurred after three injections of reserpine. The blood pressure had returned to hypertensive levels before each injection.

One additional patient, as mentioned under Methods and Materials, was given 2.5 mg. of reserpine intramuscularly for a hypertensive crisis occurring as a manifestation of a lower nephron syndrome induced by a transfusion reaction. Following the onset of the anuric phase, the blood pressure increased progressively and had attained a level of 210/110 immediately prior to reserpine administration. The blood pressure began to decrease significantly two hours after the injection and became normotensive by the fourth hour, after which normotensive levels were maintained. The urinary output increased promptly after the onset of blood pressure reduction and returned to normal 24 hours after drug administration.

Side-Effects

The most prominent side-effect during therapy with parenteral reserpine was sedation, which was manifested primarily by somnolence. It occurred in all of the patients, and the intensity was proportional to the size of the dose. Tolerance definitely developed to the sedative effect as therapy continued. If the dose was increased, however, sedation would again become more evident. The degree of somnolence was never of sufficient intensity that patients could not be easily aroused, and they always appeared completely rational except in instances of uremia or encephalopathy. A bradycrotic effect was noted in approximately one-half of the patients. This was not as marked as that observed during oral reserpine therapy, however. The incidence was particularly low in the group with glomerulonephritis, and this is probably explained by the relatively brief period of therapy in these patients. Nasal congestion was much less frequent compared to that occurring during oral reserpine therapy and was milder in intensity. Conjunctival injection was noted in the majority of the patients during the first few days of treatment but usually disappeared after this. Weakness was a common complaint, and dreams were experienced by a few patients. Mild muscle tremors were noted to appear after several days of therapy, particularly with doses of 5 mg. or more given every four to eight hours. One patient developed manifestations simulating Parkinson's syndrome, with a mask-like facies; coarse tremors of the hands, feet, and tongue, and difficulty with speech and swallowing. These occurred after he had received 5 mg. of reserpine intramuscularly every 4 hours for 10 days and 10 mg. every 4 hours for 1 day. The manifestations slowly disappeared over a period of three days after reserpine was discontinued.

General Comment

The results achieved in the three groups of hypertensive patients indicate that reserpine when administered parenterally is a relatively potent antihypertensive agent. It appears as though there are few hypertensive patients who do not obtain a significant depression in blood pressure. This antihypertensive potency is manifested in the recumbent as well as in the upright position, an attribute of considerable importance in the acutely ill and bedfast patient. The slow decrease in blood pressure which occurs and the relatively rare instances of excessive hypotension allow effective and safe therapy without particularly close supervision by medical and nursing personnel. If blood pressure reduction is desired in less than two hours, reserpine should not be used except in

combination with a more rapidly acting agent, such as hexamethonium, pentolinium, or veratrum.

The treatment of hypertensive emergencies with reserpine by the parenteral route would seem to be most useful on a short-term basis, after which the therapy can be converted to the oral route. Early conversion is desirable, since the blood pressure reduction which has been established by parenteral reserpine is slowly lost after it is discontinued. This allows time for the titration of a more potent oral drug without losing blood pressure control. The procedure for administration of reserpine parenterally in these cases is best determined on the basis of the blood pressure response obtained, since it varies in degree and duration in different patients. The most effective results were achieved when patients were placed on a regular schedule after the initial injection, on the basis of the intensity and duration of the initial blood pressure response. It usually consisted of a 6- to 12-hour schedule and a dose of 2.5 to 5 mg. The schedule and dose were later adjusted to obtain the desired blood pressure levels in so far as it was possible.

The antihypertensive effect is more potent after parenteral than after oral reserpine. This may perhaps be explained on the basis of the larger doses which were utilized for parenteral therapy. However, it is quite possible that there is insufficient absorption of reserpine from the gastrointestinal tract to achieve the antihypertensive potency which is obtainable after use of the parenteral route. This would seem to require further investigation.

The side-effects tend to become more frequent and prominent as the dose or frequency of administration of reserpine is increased. Tolerance to the sedative effect usually becomes evident after a few days of therapy at a constant dose and frequency of administration, but an increase in these will usually elicit more evident sedation. Muscle tremors and other manifestations suggesting a Parkinson's syndrome may appear after larger doses (5 to 10 mg.) given at frequent intervals, but these disappear slowly after a decrease in the dose or frequency of administration or after discontinuation of therapy.

SUMMARY AND CONCLUSIONS

Three groups of hypertensive patients were treated with parenteral reserpine on a short-term basis. The first group consisted of 14 patients with severe progressive hypertensive cardiovascular disease. In this group there were 10 patients with malignant hypertension and 4 patients with severe benign hypertensive cardiovascular disease. All the patients obtained a significant depression in blood pressure, and in nine patients (64%) the maximal depression in the supine position was in the normotensive range. Six of the 10 patients with malignant hypertension recovered from the malignant phase and are now well regulated on oral therapy. Uremia was present in four patients prior to the initiation of therapy, three of whom died as a result of uremia; one has severe uremia at the present time. The patients with severe benign hypertensive cardiovascular disease are living and are regulated on oral therapy.

The second group consisted of six patients with toxemia of pregnancy, four with severe preeclampsia, and two with benign hypertensive vascular disease and associated severe preeclampsia. Normotensive levels were attained in all the patients. All the patients recovered. No fetal complications were observed.

The third group consisted of eight patients of pediatric age with acute glomerulonephritis. Seven of the eight patients obtained a significant reduction in blood pressure, and six patients became normotensive. Six patients recovered; one progressed to a subacute stage of nephritis, and one died as a result of congestive heart failure.

The blood pressure decreased slowly after a latent period of one to four hours after the parenteral administration of reserpine and attained a maximum depression two to five hours after administration. The blood pressure depression was manifested in the recumbent as well as the upright position. Excessive hypotension was rare.

The side-effects consisted of sedation, bradycardia, weakness, dreams, and conjunctival injection. Muscle tremors developed after several days of therapy with large doses (5 to 10 mg.) administered at intervals of four to eight hours, and in one patient a Parkinson-like syndrome developed. This subsided completely after discontinuation of the drug.

Reserpine administered parenterally is an effective and safe agent for the treatment of hypertensive emergencies on a short-term basis.

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Idiopathic Thrombophlebitis

Report of Two Cases with No Evidence of Venous Involvement in Acute Phase

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Thrombophlebitis is a relatively common disease. In some instances it is a component or complication of specific clinical entities which do not involve primarily the venous system; in others it results from direct infection of the vein wall, while in still others it appears as an isolated affection without any discoverable underlying illness or cause. It is with this last type, so-called idiopathic thrombophlebitis, that this paper is concerned.

We have recently had the opportunity to study two young men who presented themselves with an undiagnosable illness, the features of which were strongly suggestive of an infection. No evidence of phlebitis was present in the acute phase, and this disease was not suspected until many weeks after recovery, when evidence of a severe degree of venous occlusion became apparent. It is the purpose of this paper to report the clinical findings and course in these two cases and to present evidence that they constitute a previously undescribed syndrome, to review the recorded literature pertaining to idiopathic thrombophlebitis, and to point out that the various syndromes which have been described probably are merely variants of a single entity.

REVIEW OF LITERATURE

The syndrome of idiopathic thrombophlebitis has been known since 1845, when it was first reported by Jadioux.[1] He described a 20-year old man who, without any preceding illness, developed pain and a "red cord" in one thigh, which was followed, after an unspecified period, by occlusion of the major veins and edema. Repeated relapses of pain and discoloration of the leg occurred over a period of four months, after which all manifestations disappeared and did not return. Since the publication of this paper, there have been numerous reports presenting a bewildering variety of lesions described as idiopathic phlebitis, periphlebitis, and thrombophlebitis. In most instances, an attempt has been made to exclude known causes of thrombophlebitis, but patients who subsequently were found to have carcinoma, tuberculosis, or specific vascular lesions such as Raynaud's disease have sometimes been included.

Phlebitis, Periphlebitis: Phlebitis Migrans.—The simplest form of idiopathic vein involvement is a phlebitis or periphlebitis, which is manifested mainly by the appearance of tender "cords" in the arms, legs, chest, or abdominal wall, occasionally associated with localized edema. Rarely, nodule formation occurs; these lesions tend to migrate either centripetally [3] or centrifugally.[6] Superficial phlebitis of the thoracic and abdominal wall, often referred to as Mondor's disease, despite the fact that it was known for many years before Mondor described it in 1939,[7] is characterized by the presence of tender "cords" along the course of superficial veins. These appear without any prior illness, are painless, and subside without treatment.

Chest pain was the outstanding feature in six patients with lateral thoracic phlebitis described by Daniels.[8] In one instance the discomfort was so great that pleurisy was sus-

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pected until the characteristic thickened vein coursing from the nipple line to the xiphoid process became apparent. The symptoms and signs of venous involvement persisted for only a few days. This lesion may be confused with the phlebitis which is sometimes associated with mammary carcinoma, but it is distinguished from the latter by its short duration and the fact that it occurs in males as commonly as in females. Robinson [9] has reported the same syndrome in women in whom no pain was present and in whom it was at first mistaken for a tumor. Lateral thoracic phlebitis is usually not accompanied by fever, constitutional signs, or leucocytosis and is different from "Mondor's disease," in which the venous involvement tends to be more diffuse. Instances of simultaneous phlebitis of the lateral thoracic wall and arm have been recorded.[7]

Evidence that the "cords," which are the outstanding feature of this type of phlebitis, are veins and not arteries or lymphatic vessels has been presented by Lunn and Potter,[7] on the basis of biopsy studies. The fibrous "cords" were found in association with other vessels and were observed to be branches of veins, other portions of which were unaffected by the process. The lesions were fibrotic and contained rings of smooth muscle, sparse elastic fibrils, collagen, fibroblasts, and erythrocytes. Other segments of the vessel exhibited only intimal swelling and subintimal accumulations of amorphous material; in some areas, thrombosis and recanalization were observed.

Harkavy [3] and Tidy [10] described another form of phlebitis, involving primarily superficial veins. Phlebitis migrans, believed by Tidy to be a distinct entity because of the absence of thrombosis, the outstanding feature of idiopathic thrombophlebitis, is a wandering affection of the small veins of the forearm in which spindle-shaped nodules, 2 to 3 cm. in length, appear along the course of the involved vessels. The nodules are tender and are sometimes surrounded by edema. Both thrombosis and periphlebitis have been demonstrated in this syndrome by Harkavy [3] and Lunn and Potter,[7] however. These findings suggest that phlebitis migrans and idiopathic thrombophlebitis are probably closely related.

Harkavy [3] reported cases of migrating thrombophlebitis involving superficial veins in which nodule formation, signs of inflammation, and edema were present and in which spread of the process from one portion of the vessel to another was accompanied by fever. The disease was not limited to the small veins but also affected the larger ones of the arm. This syndrome was observed in patients with tuberculosis, gout, syphilis, "toxic and cachectic states," acromegaly, and sensitivity to shell fish. Two anatomically different venous lesions were demonstrable. In one, an inflammatory process involved the outer and middle walls of the vessel, with no apparent intimal reaction. There was no limitation to the flow of blood, and healing left no residual changes. In the other, all layers of the involved vein were affected and thrombosis was the rule. Although recanalization was demonstrable, residual fibrotic "cords" were common. Microscopic study of the nodules revealed them to be composed of veins with normal intimal layers but with thickened medial walls in which there was a subacute inflammatory process consisting of lymphocytes, connective tissue, and newly formed capillaries. There appears to be little difference between the syndrome described by Harkavy [3] and that reported by Tidy.[10] The inflammatory response in the veins was the same in the patients studied by Lunn and Potter [7] and by Harkavy.[3]

Migrating Phlebitis, Thrombophlebitis.—Occlusion of small veins is rarely likely to produce more than local manifestations; owing to the abundance of collateral channels, even edema is uncommon. When large peripheral or superficial vessels are involved in an inflammatory process, more pronounced changes usually occur; edema in the vicinity of the vein or in the areas drained by it is common. A peculiar migrating phlebitis, similar to that described by Harkavy except for the size of the vessels involved, was reported by Briggs [4] in 1905.

In this syndrome, red and tender "cords" appeared along segments of the internal saphenous vein. Pain was usually the first symptom; the skin overlying the affected segment was red and tender. The process began at the distal end of the vessel, and, over a period of weeks or months, it migrated upward toward but never beyond the inguinal ligament. Although only one portion of the vein was involved in the acute inflammatory process at one time, a distal residual fibrous "cord" was usually present. Fever and leucocytosis were absent. The disease was benign, left no serious sequelae, and was not likely to be complicated by pulmonary embolization, even when the axillary, brachial, or femoral veins were involved. Although it has been pointed out [3] that these cases were not idiopathic, since many of the patients had typhoid fever, this criticism does not appear to be valid, since a careful perusal of Briggs' data reveals that this infection was a complicating factor in only two instances, in both of which it occurred more than 10 years prior to the development of thrombophlebitis.

Daguillon,* in 1894, pointed out that the prognosis for migratory thrombophlebitis was poor because of the ever-present danger of pulmonary embolism. In a study of a number of cases over a 10-year period, Ackerman and Estes [5] found that one-third had single episodes of thrombophlebitis, limited to the lower extremities. The others suffered recurrent attacks, with involvement of veins of both the legs and the arms. The age range and sex distribution in both groups were the same. The commonest sequel was chronic venous insufficiency and persistent lymphedema; this occurred in 76% of those in the larger group and in 45% of the smaller one. About one-third of all the patients had pulmonary emboli. Mesenteric thrombosis, "heart attacks," and "cerebrovascular accidents" were recorded in those with recurrent phlebitis; the incidence of complications in this group was 90%, while among the persons with single episodes of thrombophlebitis it was 62%.

Peripheral and Visceral Thrombophlebitis Migrans.—Up to this point, the discussion has been concerned primarily with phlebitis affecting a single vessel or a group of vessels in the extremities. There are reports, however, of involvement of veins of varying size and in different areas of the body in one person; thus, phlebitis of the lateral thoracic, cephalic and saphenous veins has been observed in the same patient.[7] Harkavy [8] made the comment that, in his experience, no vein was spared, although, in the majority of cases, the peripheral vessels were the ones most affected.

Not only may there be dissociation of lesions in the peripheral venous system, but both visceral and peripheral involvement may occur in the same person. Visceral phlebitis was first reported by Paget,† in 1866. It is a rare disease.[11] Walker [12] reported a group of 10 cases, collected from the literature, each of whom had idiopathic thrombophlebitis involving multiple peripheral and visceral vessels. The patients described by Walker and by Kletz [13] had true migratory phlebitis, with sequential involvement of three different veins. The true incidence of visceral phlebitis is impossible to establish, because the manifestations are often transitory and vague. Unless pathologic examination is carried out, it is often impossible to confirm clinical impression. This is illustrated by a case described by Moorehead and Abrahamson [14]: A woman was stung on the tip of the finger by a bee and subsequently developed cephalic vein phlebitis. Following this, signs and symptoms of pulmonary infarction appeared. These lasted only a short time but were quickly succeeded by severe abdominal pain, spasm of the abdominal wall, decreased bowel sounds, fever, and leucocytosis. A diagnosis of mesenteric thrombosis was made; recovery was uneventful. After several weeks of good health, frank thrombophlebitis of the left saphenous became apparent. Although the pulmonary infarction might have been due to embolization from

* Thèse de Paris, 1894, cited by Briggs.[4]

† Paget, J.: St. Bartholemew Hosp. Rep. 1866; cited by Gerber and Mendlowitz.[16]

the cephalic vein, involvement of the mesenteric vein could not be explained on this basis and was presumed to have been due to visceral phlebitis, although the diagnosis could not be proved.

There is a better basis for the diagnosis of visceral vein thrombosis in a boy described by Gottlieb and co-workers.[15] This patient had an unusually severe and protracted course after thrombophlebitis of one leg first appeared, at the age of 13. There were numerous recurrences, always associated with fever, pain, and swelling. By the age of 20, this young man had been hospitalized numerous times because of chronic lymphedema of the lower extremities accompanied by superficial infections and ulcerations. He had also experienced repeated episodes of pleural effusion and ascites, which were treated by repeated aspiration of fluid, diuretics, and control of sodium ingestion. Extensive studies revealed no underlying disease process or abnormalities of the clotting mechanism. Localized phlebitis complicated every venipuncture.

Visceral thrombophlebitis has been discussed most thoroughly by Gerber and Mendlowitz.[16] Their analysis of the clinical and pathologic findings demonstrates the extremely variable syndromes produced by thrombosis of visceral veins. As might be expected, symptoms attributable to disorder of a number of organs are likely to develop simultaneously. An example of this is a patient who had thrombocytopenic purpura, anemia, leucopenia, splenomegaly, polyserositis, and a facial rash; a diagnosis of disseminated lupus erythematosus was made. At autopsy, however, extensive thrombophlebitis of multiple visceral veins was the only finding. The syndrome of repeated attacks of thrombocytopenia has been explained on the basis of a reduction in the number of circulating platelets by their withdrawal from the circulation into extensive visceral vein thromboses at a faster rate than they can be produced.[17] In such cases, large portions of many major venous channels have been completely obliterated. The greater part of the inferior vena cava and the portal and mesenteric veins may be involved in this extensive reaction.

Disseminated as these lesions may be, Gerber and Mendlowitz[16] were unable to verify a single instance of involvement of the pulmonary or cardiac veins. Cor pulmonale associated with visceral thrombophlebitis is probably secondary to pulmonary infarction; "heart attacks" consisting of arrhythmias and anginal pain without electrocardiographic changes have been reported but are probably not causally related. All of the signs of constrictive pericarditis may occur during the course of visceral thrombophlebitis when the vena cava is occluded.

Idiopathic migratory thrombophlebitis affects primarily medium-sized and small veins, usually of the lower extremity; as a rule, only short segments of a vessel are involved at one time, except when there are visceral complications. Anatomical studies[16] reveal venous and perivenous inflammation, the exudate consisting predominantly of polymorphonuclear cells early and of lymphocytes, monocytes, and even eosinophiles late in the course of the disease. The location of the changes does not indicate whether the process starts inside or outside the vein. The lesions in the visceral vessels are identical with those in the peripheral ones, although they appear to be accelerated in the former. In this type of thrombophlebitis, as in some of the others, the duration is short and remission of symptoms is the rule; if thrombosis occurs, recanalization frequently takes place. Collateral channels are often sufficiently ample during the period of venous occlusion. When extensive involvement takes place in organs in which an adequate collateral circulation is not present, serious complications may appear.

REPORT OF CASES

Case 1.—C. F., a 16-year-old white boy, entered a hospital outside of Boston because of pain in the legs and abdomen. He had been well until about one week previously, when, after climbing a mountain, he developed rather severe pain in the back and in both thighs. He attributed this to a "strain" incurred during physical activity. Two days before hospitalization abdominal pain appeared; this

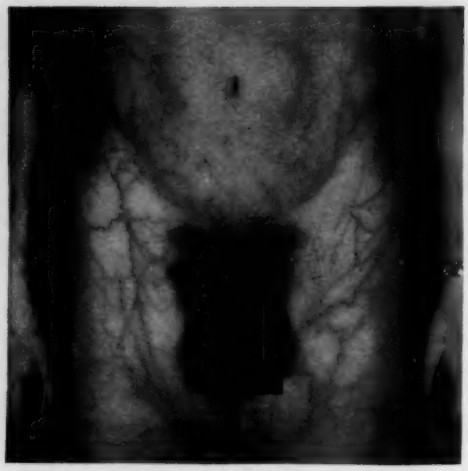


Fig. 1.—Infrared photograph illustrating the extent of collateral vein utilization appearing at the end of the latent period before the development of edema.

rapidly became so severe that walking had to be carried out in a stooped position. There had been no nausea or vomiting and no change in bowel habit.

Physical examination at the time of admission to the hospital revealed a thin apprehensive young man. There was a moderate degree of fever. The only abnormal findings were tenderness in both thighs and calves and tenderness of the abdomen, with an impression of "fullness" to the right side. A moderate leucocytosis was present. The urine was normal. A diagnosis of appendicitis was made, and operation was performed. The appendix was entirely normal, and there was no evidence of intra-abdominal disease.

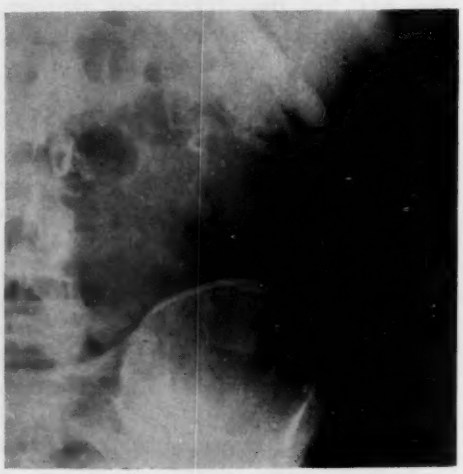
Postoperatively, the course was characterized by increasingly severe pain in the thighs and calves, continuing fever, and leucocytosis. X-rays of the lumbosacral and thoracic spines were normal. No rise in agglutinins for Salmonella typhi, the paratyphoid bacilli, or Brucella was detectable. On the fourth postoperative day the patient was seen by one of us (L. W.) because it was thought that he had poliomyelitis. Physical examination at this time revealed some stiffness of the back and marked tenderness to even mild palpation of the calves and, particularly, of both thighs. There was considerable pain in both hip and knee joints on attempted movement of the legs. There was no evidence of venous involvement and no edema of the lower extremities. Fever was of moderate degree. The abdomen, heart, and lungs were not remarkable. There was moderate leucocytosis. Lumbar puncture revealed the spinal fluid to be entirely within normal limits. During the following week all manifestations disappeared, and the patient was discharged from the hospital three weeks after entry.

This young man was seen (L. W.) 11 months later because, about one month previously, he had become aware of increasing prominence of the veins of the lower extremities. Examination revealed marked varicosities and edema of both lower legs and thighs. He was referred to Dr. Charles H. Robertson, at the Massachusetts Memorial Hospitals, who performed high saphenous ligation and vein stripping. There has been no recurrence of manifestations of venous system disease in the following 18 months.

Case 2.—P. S., a 21-year-old white man, was admitted to the Haynes Memorial Hospital because of fever and severe pain in the thighs. His illness started about one month previously with mild back pain. This was constantly annoying but did not restrict his activity for about a week. He was then forced to stop work because of the increasing severity of the discomfort. Two weeks before admission he had to go to bed because of severe aching pain in both thighs and high intermittent fever. He was investigated by his family physician for trichinosis, infectious mononucleosis, and infectious hepatitis. The presence of none of these diseases could be confirmed; he was referred to the hospital for further study.

On admission, the patient complained of pain in the legs. The temperature was 99.6 F rectally; the pulse rate, 70, and the blood pressure, normal. Physical examination was completely unrevealing except for tenderness of both calves and thighs

Fig. 2.—Venogram taken after the injection of 30% sodium acetrizoate (Urokon sodium) into a vein on the dorsum of the foot. It was taken at the same time as the infrared photograph, Figure 1, and demonstrates the tortuous and dilated collateral channels over the lower anterior abdominal wall after occlusion of the femoral veins.



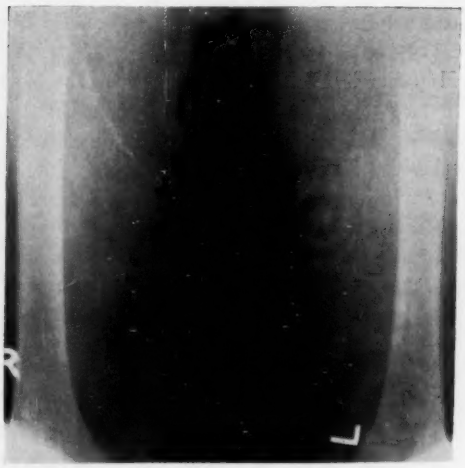


Fig. 3.—This venogram was obtained at the same time as Figure 2 and shows primarily the absence of filling of the deep veins of both lower extremities. Only the small superficial veins have filled with the radiopaque dye. Obstruction of the femoral veins on each side prevented filling of the major venous channels.

and limitation of motion at both hip and knee joints by pain. No redness or edema, or other manifestations suggestive of an inflammatory process, were present.

Urinalysis was normal. The white blood cell count was 12,200, with 60% polymorphonuclear cells, 20% lymphocytes, 6% monocytes, and 5% eosinophiles. X-ray of the chest and electrocardiogram were normal. Widal, heterophile, and Brucella agglutination were negative.

The patient was afebrile during his entire hospital stay. However, he continued to suffer from constant severe aching pain in both thighs which was aggravated by even slight motion. At no time was there any visible evidence of phlebitis. Salicylates produced relief of pain; because of the complaint of considerable discomfort in and around the knee and ankle joints and the relief produced by the salicylates, the possibility of rheumatoid arthritis and gout were considered but not proved. Discomfort gradually abated, and the patient was discharged from the hospital to be followed by his family physician.

During the first month at home the mild aching discomfort in the thighs disappeared. About two months after he left the hospital a number of dilated, tortuous, and prominent veins of the legs and anterior abdominal wall suddenly appeared; it was the impression of the patient that they became apparent "over night." He was seen by one of us (L. W.) within a few days of the appearance of the dilated veins, and their presence was confirmed. Infrared photographs, made of the anterior abdominal wall, chest, and legs, revealed the presence of large collateral channels in these areas (Fig. 1). Venography carried out at the same time (Figs. 2 and 3) showed the superficial venous system to be outlined on both sides as far as the junction of the long saphenous vein with the femoral vein; the dilated collateral vessels over the anterior abdominal wall were easily demonstrable. The inferior vena cava and iliac veins were not visualized.

Several weeks after the collateral channels were noted, edema of the extremities first became apparent; it began over the feet and gradually extended upward until the whole of both legs was involved.

Venograms were made five months later (Figs. 4 and 5). At this time, the injected dye revealed a normal-appearing venous system in the right lower leg. The right popliteal vein and its branches were well visualized. In the proximal portion of the deep venous system on this side there was irregularity within the lumen of the femoral vein, consistent with recanalization of a thrombus. The external iliac veins were faintly visible in the pelvis. Study of the left leg revealed outlining of only a

Fig. 4.—This venogram was obtained five months after occlusion of the femoral veins became apparent and shows the appearance of the right leg, where a normal-appearing deep venous system is outlined. Recanalization first appeared on this side. Irregularity within the lumen of the proximal portion of the right femoral vein was demonstrated. This feature is not visible here; the films showing it were not suitable for reproduction.

portion of the deep venous system of the calf in its distal third. The long saphenous vein was filled, and its point of entrance to the deep venous system was visualized. There was no filling of the popliteal branches. These roentgenograms were interpreted as indicating recanalization of the deep venous system on the right and persistence of occlusion of these vessels on the left. At the time these studies were made there was no longer any swelling of the right leg; several more months were required for the left leg to become normal. There were no further episodes suggestive of thrombophlebitis during the following year, the period during which the patient was observed.

COMMENT

The clinical pictures observed in the patients described above were strikingly simi-

Fig. 5.—This venogram, taken at the same time as Figure 4, shows filling of the popliteal and the saphenous system on the right, where recanalization of the femoral vein had taken place, whereas on the left only the superficial veins have filled with the contrast medium.

lar. Both were young men who were entirely well until they developed back ache followed by manifestations of infection and marked pain in the legs. These symptoms lasted approximately two to three weeks. After several months of apparent good health, evidence of a marked degree of venous occlusion in the lower extremities became apparent. Most striking was the absence of clinical findings such as edema, discoloration, prominence of veins, or tenderness or nodules along the course of vessels in the acute phase, suggestive of thrombophlebitis. It is also important to point out that, as far as could be ascertained during the 18 to 30 months of observation, neither of the patients had any of the diseases listed in the Table; this allows the classification of these cases as "idiopathic."

An attempt to reconstruct the course of the disease suggests that the following events may have occurred: The earliest lesion was probably a nonoccluding deep phlebitis of the legs with no external evidence of inflammation. As the active process subsided, pain and fever disappeared. It is possible that the vein disease persisted or, if it did not, then it left the wall of the involved vessel damaged; this led to slowly progressive thrombosis which, over a period of several

Etiology of Thrombophlebitis *

I.	Infections
	Scarlet fever
	Upper respiratory tract infections
	Septicemia
	Influenza
	Pelvic inflammatory disease
	Meningitis
	Encephalitis
	Varicella
	Variola
	Dysentery
	Brucellosis
	Erysipelas
	Pyogenic arthritis
	Pyelonephritis
	Tuberculosis
	Pneumonia
	Cellulitis
	Syphilis
	Typhoid fever
	Cholera
	Typhus
II.	Neoplasms
	Carcinoma of the stomach
	Carcinoma of the pancreas
	Carcinoma of the lung
	Metastatic carcinoma of the brain
	Sarcoma of bone
III.	Metabolic diseases
	Gout
	Diabetes mellitus
	Hyperthyroidism
	Phenobarbital poisoning
	Dehydration (mercurial diuresis)
IV.	Cardiovascular disorders
	Hypertension
	Heart disease with congestive failure
	Buerger's disease
	Raynaud's disease
V.	Hematologic disorders
	Polycythemia vera
	Postsplenectomy thrombocythemia
	Hyperfibrinogenemia
	Megakaryocytic aleucemic myelosis
	Idiopathic thrombocythemia
VI.	Trauma
VII.	Allergy (?)
VIII.	Idiopathic

* References 3, 5, 16, and 18-21 and Paget, J.: *St. Bartholemew Hosp. Rep.*, 1866, cited by Gerber and Mendlowitz.[16]

months, produced complete occlusion of the veins. With decrease in size of the venous lumen, a greater burden was placed on collateral channels, which became widely dilated. As these pathways became ineffective, signs of venous insufficiency with marked edema became prominent. After many months, recanalization of the involved vessels took place and normal blood flow was restored.

A comparison of the syndrome described in these patients with the cases previously reported as idiopathic thrombophlebitis in the literature reveals that the essential difference is the total absence of signs of involvement of the venous system during the acute phase of the illness in our cases. In the recorded descriptions, regardless of the name which has been attached to the disease, obvious evidence of phlebitis of the chest or abdominal walls or the extremities has been the most striking feature. In visceral thrombophlebitis, on the other hand, pain and manifestations of infection have been outstanding; without surgical exploration or autopsy studies, it is impossible to demonstrate disease of the veins in these instances. The appearance of venous occlusion later confirms the primary illness as one which involved the veins in the legs in the cases reported in this paper. The absence of manifestations of phlebitis early in the illness distinguishes them from other described instances of thrombophlebitis and suggests that they represent a new syndrome in the idiopathic type of this disease.

The establishment of a diagnosis of idiopathic thrombophlebitis requires that all known causes of this disease be ruled out. This is sometimes impossible at the time when the venous disease is prominent. In not a few of instances, the first impression of idiopathic phlebitis is changed, weeks or months later, because of the appearance of signs of some other illness in which venous inflammatory reactions occur. The diseases which must be considered and ruled out, whenever possible, before the diagnosis of idiopathic thrombophlebitis can be accepted are listed in the Table. In the two patients reported in this paper no evidence of the presence of any of these conditions was obtained after one and one-half years and after two and one-half years, respectively. While phlebothrombosis was considered as a possible cause of the illness in these young men, the absence of provoking clinical situations and the appreciable fever which was present early were thought to be sufficient grounds for ruling out this entity.

An analysis of the different clinical syndromes which have been described in which idiopathic thrombophlebitis has been found to be the underlying lesion suggests an analogy between this malady and a totally dissimilar affection, erythema multiforme. This disease is characterized by a wide variety of manifestations, which range from transient and mild skin rashes of multiple morphology, without any constitutional reaction, to situations in which the entire skin, most of the mucous membranes, and the conjunctivae are the site of numerous bullae containing hemorrhagic fluid in persons who are extremely ill, have high-grade fever, and rarely die. Between these two extremes are found clinical pictures of all degrees of severity, persistence, and tendency to recurrence. Many of the syndromes which are now recognized as variants of erythema multiforme were for many years given specific names and considered to be entities. As in thrombophlebitis, the etiologic background of erythema multiforme is multiple; infections (particularly viral pneumonia, herpes simplex, and streptococcal invasion) or allergy to drugs (trimethadione, U. S. P. [Tridione], barbiturates, and the sulfonamides) precede the appearance of the skin lesions in some cases, while in others no specific provoking incident can be discovered.

On the basis of this analogy, we venture to suggest that the various syndromes which are characterized by acute venous inflammation and evidence of occlusion of vessels without any discoverable cause are not distinct entities but represent variations in the clinical pictures which may occur with idiopathic thrombophlebitis. Differences in the anatomical location; in severity, as illus-

trated by the presence of fever and leucocytosis in some cases but not in others; in duration; in degree of occlusion of the involved veins, and in the tendency to recurrence do not appear to be sufficient grounds for attaching specific names to some of the syndromes nor for presuming that they are etiologically or clinically distinct. For this reason, the cases reported in this paper have been considered examples of a previously undescribed variant of idiopathic thrombophlebitis.

SUMMARY AND CONCLUSIONS

Two cases are described in which prodromal symptoms of backache were followed by severe pain in the thighs and calves, fever, and leucocytosis, without signs of phlebitis in the acute phase. Recovery occurred spontaneously and was followed months later by complete venous occlusion in the legs. In one patient, recanalization of the occluded vessels took place and was complete about seven to eight months after the onset of his illness; in the other, vein ligation and stripping was required one year later because of large varicosities of both legs.

Idiopathic thrombophlebitis is a single disease entity. The various forms which have been described under a variety of names, depending on anatomical location, severity, and outcome, are probably only quantitative variants of the same syndrome.

The cases reported in this paper probably constitute a new syndrome in idiopathic thrombophlebitis, because of the lack of signs of phlebitis in the acute phase of the disease, the long latent period between the onset of the illness and the appearance of signs of venous occlusions, and the failure to discover any underlying process which might have been responsible for the venous involvement.

Dr. Walter H. Lacey, of Keene, N. H., gave permission to study and report the first case, and Dr. Morris Ringer, of Hull, Mass., referred the second case to us for study and aided in the follow-up investigations.

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Embolization of Basilar Artery by Myocardial Fragment

Report of a Case

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Cerebral embolism is one of the three common types of cerebral vascular accident (hemorrhage, thrombosis, embolism). All are acute in onset and severely damaging in their effects, and all offer a uniformly poor prognosis. Of these three, embolism must invariably be considered as the manifestation of an underlying disease rather than as a separate primary disease process; therefore therapy must include measures intended to alleviate the primary pathological process.

The enumeration of materials which may form emboli is an unending task and includes everything from bubbles [1] to bullets.[2] The following outline is representative of the variety of cerebral emboli which have been reported in the literature:

1. Thrombi
   - A. Septic
   - B. Bland
   - C. Fibrin
2. Tissue fragment emboli, originating within the victim's body
   - A. Tumors
     - (1) Myxoma of heart [3]
     - (2) Small secondary tumor emboli
   - B. Atheromatous material
   - C. Valvular vegetations and calcifications
   - D. Marrow particles
   - E. Amniotic fluid
3. Foreign body emboli
   - A. Air
   - B. Fat and oil particles
   - C. Chemicals, etc.
     - (1) Soap solutions (followed washing of a postpartum uterus)
     - (2) Estrogens
     - (3) Iodized oil, U. S. P. (Lipiodol)
   - D. Pathogenic organisms
     - (1) Bacteria
     - (2) Actinomyces
     - (3) Parasites
       - (*a*) Trypanosoma brucei
       - (*b*) Parasitic ova, unspecified
   - E. Unspecified [4]

In all these reports there is no case in which the embolus actually consists of or includes heart muscle, as is true in this case, although "myxomas" of the heart forming cerebral emboli have been reported.[5]

Undoubtedly it is axiomatic that the commonest thrombotic embolus to the cerebral arteries is of cardiac origin * or, in rare instances, from some venous thrombus via a patent foramen ovale or, conceivably, from a pulmonary infarction including thrombosis of the pulmonary veins. Thrombotic emboli originating in the heart itself are of two types; first, septic fragments from the vegetations of endocarditis; second, nonseptic fragments, rarely from rheumatic endocarditis, more commonly from the mural thrombi associated with cardiac arrhythmias or myocardial infarction. The latter is commonest and results in focal or massive cerebral sof-

Dr. Elwyn E. Stiles provided the clinical material cited.

Resident in Pathology, Glendale Sanitarium & Hospital (Dr. Harder); Associate Professor of Pathology, College of Medical Evangelists School of Medicine, and Pathologist, Glendale Sanitarium and Hospital (Dr. Brown).

* References 5 and 6.

tening of varying magnitude in accordance with the size and point of lodgement of the embolus.

This case is reported because two most unusual features were found in the same patient, i. e., embolism of the basilar artery and inclusion of heart muscle in the embolic material. Embolism of the basilar artery, though reported as early as 1859,[7] is rare, because both vertebral arteries and both posterior communicating arteries are of smaller caliber than the basilar artery and an embolus large enough to occlude the basilar lumen could not enter any of its tributaries.[8] In this case one vertebral artery was rudimentary in nature while its fellow had a lumen of sufficient size to compensate for this and was therefore larger than the basilar artery itself.

REPORT OF CASE

The patient, a 29-year-old Caucasian man, was admitted to the hospital at 7:20 a.m., June 24, 1952. He had been unconscious for half an hour, and the following history was obtained from his physician, his mother, and his roommate. About 6 a.m. the patient awakened his roommate by peculiar involuntary twitching of hands and legs. When seen by the attending physician, almost immediately thereafter, he complained of headache, dizziness, and numbness of his entire body. His speech was thick; answers to questions were inaccurate; the right pupil was dilated and irregular, and he had bilaterally positive Babinski reflexes. He was rapidly losing consciousness and when seen by the intern (immediately after admission) was unable to provide a history or answer questions.

At the age of 16 the patient had an acute attack of typical rheumatic fever with joint pains and myocarditis. Since then he had had frequent episodes of auricular fibrillation. When first seen by his attending physician, six weeks previously, he had an acute infection (site or nature not stated) and acute heart failure with auricular fibrillation. The infection was cleared in three days with antibiotics, primarily penicillin. Quinidine in small doses reverted the heart rhythm to normal. A mitral commissurotomy at that time was not considered advisable by surgical consultants. The use of digitalis in place of quinidine was tried, but this was followed by the prompt return of auricular fibrillation. Following this treatment he went to his mother's home in another city, returning the evening before onset of the present illness.

A physical examination showed the patient to be an unconscious slender well-developed and well-nourished Caucasian man with warm dry skin, involuntary twitching of the extremities, hyperactive superficial and deep reflexes, and bilaterally positive Babinski reflexes. Examination of the head was negative except for dilated pupils, the right larger than the left, and the absence of pupillary light reflexes. Funduscopic examination showed no abnormalities. The neck was slightly stiffened. The lungs were clear to percussion and auscultation. The heart was not enlarged to percussion. The rhythm was slow and irregular, with numerous premature beats. An apical Grade II systolic murmur and a faint diastolic apical murmur were heard. The abdomen was normal. The extremities were twitching and had hyperactive deep reflexes but were otherwise normal. A neurologist was immediately consulted, who noted that, in addition, there were involuntary spasms of the extremities. He performed a lumbar puncture, which yielded clear fluid under no increased pressure. Laboratory examination of this fluid showed no white cells or increased globulin. A bilateral stellate ganglion block gave only fleeting improvement. Later in the day the patient became flaccidly paralyzed but otherwise his condition did not change. On the following day he showed marked deterioration, and no breath sounds could be heard over the right lung. Portable chest x-rays showed hazy infiltration of the right lung field, not inconsistent with pulmonary embolism. A repeat x-ray the following day showed definite pneumonitis with diffuse haziness in the right upper lung field. His condition became progressively worse and he died at 8:20 p.m., June 26, 1952, without regaining consciousness, about 62 hours after the known onset of symptoms.

A partial autopsy was done by the coroner's office because the patient had been involved in a minor traffic accident six weeks before the onset of the final illness. After the coroner's investigation the hospital necropsy was performed. No evidence of cranial trauma or hemorrhage was present. The arterial pattern of the brain was unusual in that the right vertebral artery was large, while the left was small and rudimentary, and the basilar artery appeared to be merely a continuation of the right vertebral artery. At a point immediately proximal to the origin of the superior cerebellar arteries, the lumen of the basilar artery was found to be completely occluded by a gray-brown blood clot with suggestive lines of Zahn. This thrombus extended for about 8 mm. into the left superior cerebellar artery, filled the remaining terminal extent of the basilar artery, and also occluded the initial 3 mm. of the right posterior cerebral artery. No other vascular anomalies or obstruction were noted in the circle of Willis, its tributaries, or its branches. All the vessels were free from atherosclerosis. Sections of the brain stem immediately deep to the occluded segment of the basilar artery showed a comma-

Fig. 1.—Pedicled mural thrombus of left atrium.

shaped red-black 13 by 8 mm. area of hemorrhagic softening extending posteriorly, roughly parallel to the anterior-posterior axis of the brain stem and extending vertically for 2.4 cm. within the pons. No cerebral or cerebellar lesion was noted. The heart was greatly enlarged but weighed only 370 gm. This enlargement was almost entirely due to tremendously dilated atria; the right was the larger. The right atrium was free of thrombi, but the left contained a small amount of mural thrombus in the appendage and a small, rough, rounded, 1.3 cm. thrombus dangling in the lumen by a very narrow 1.6 cm. stalk (Fig. 1). No other mural thrombi were found, and no recognizably antemortem defect of the atrial wall was found, though such may have been obscured by the partial anatomical investigation conducted by the coroner. The valves were all normal except the mitral, which was markedly narrowed by thickened fibrotic valve cusps, held in a retracted position by short, thick, fibrous chordae tendineae. Cut surfaces of the myocardium showed no evidence of infarction or other significant gross lesion. The lungs showed numerous discrete, dark

Fig. 2.—Cross section of basilar artery at the origin of the superior cerebellar artery, showing occlusion of both by embolus.

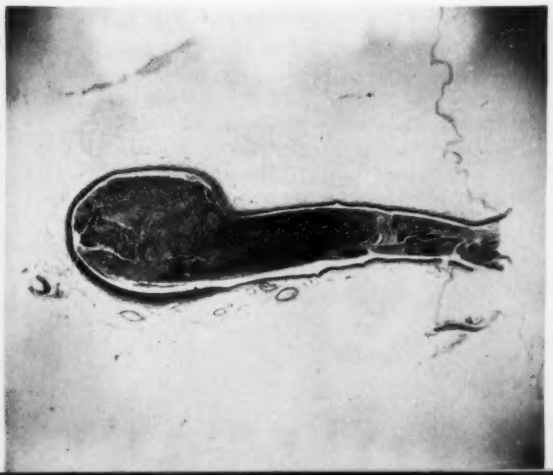

Fig. 3.—Embolic fragment of myocardium lodged in left superior cerebellar artery.

brown-black areas of consolidation in the right lung, and generalized edema and congestion of both lungs. The remainder of the autopsy was essentially negative.

Microscopic Examination.—Heart: Section of the myocardium showed only occasional small loose perivascular foci of cells, without definite Aschoff-body construction. Section of the left auricle showed a partially organized, laminated thrombus attached to the edematous endocardium by a long pedicle (Fig. 1). The mitral valve was a relatively acellular, dense, collagenous, fibrous structure, with thick chordae tendineae but no definite Aschoff bodies.

Basilar Arteries: Cross section of the basilar artery at the origin of the left superior cerebellar artery showed both vessels occluded by a tight-fitting, but unattached, laminated thrombotic mass (Fig. 2). The distal portion of this embolus extended into the superior cerebellar artery and included degenerating cardiac muscle fibers surrounded by loose connective tissue strands and an occasional small vessel (Fig. 3).

Fig. 4.—Hemorrhagic infarction in pons adjacent to embolic site in basilar and superior cerebellar arteries.

Pons: Section from pons immediately deep to the occluded basilar artery showed hemorrhagic softening and edema (Fig. 4).

Lung: Sections showed edema fluid, red cells, "heart failure" cells, and massive polynuclear infiltration in some areas. In the central portion of these areas the alveolar walls were indistinguishable.

Pathological Diagnoses:

1. Rheumatic heart disease, inactive, with mitral stenosis
2. Mural thrombus of left auricle
3. Embolus containing heart muscle, lodged in the basilar artery; encephalomalacia of pons with hemorrhage due to embolism
4. Bronchopneumonia

COMMENT

We see here a patient with rheumatic heart disease who developed symptoms suggestive of cerebral embolism and the clinical syndrome referred to as "basilar artery syndrome."[9] The clinical picture is not unusual, but its etiology is unique in that lodgement of an embolus in the basilar artery is very uncommon and the inclusion of myocardium in an embolus has not been previously reported (Fig. 3). The mechanism of the latter is not entirely clear, but it is possible that the sudden strain of an unusually strong contraction tore away a pedicled thrombus with attached atrial wall fragment similar to the one that was found in the left atrium (Fig. 1).

SUMMARY

A case is described in which an embolus containing heart muscle lodged in the basilar artery. No reference to a similar case has been found in the standard medical indices. An additional unusual feature is that the embolus was enabled to lodge in the basilar artery because of the congenital enlargement of one vertebral artery.

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Vitamin B12 Deficiency Following Total Gastrectomy

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Intrinsic factor is essential, in man, for the absorption of the small amounts of vitamin B_{12} normally present in the diet. There is evidence that the stomach is the only site of secretion of intrinsic factor.[1] Following total gastrectomy, the human would be expected to experience difficulty in the absorption of vitamin B_{12} and eventually to develop a vitamin B_{12} deficiency state.

Difficulty in absorption can be readily demonstrated by giving such patients small oral doses of radioactive (CO^{60}) vitamin B_{12} and estimating the amount of radioactivity excreted in the feces.* In normal persons a considerable amount of the dose is absorbed, whereas in gastrectomized patients most of the administered radioactivity subsequently appears in the feces. The administration of a source of intrinsic factor together with the radioactive vitamin B_{12} results in improved absorption and lessened fecal radioactivity.

Megaloblastic anemia may be a late complication of total gastrectomy. In four such patients, Mollin and Ross found low serum concentrations of vitamin B_{12}.† Hall [7] describes a case of megaloblastic anemia which developed three years after total gastrectomy and responded to vitamin B_{12} therapy. MacDonald and co-workers [8] describe two cases which developed macrocytic anemia two and five years, respectively, following surgery. They collected the records of 46 patients who had survived a minimum of three years after total gastrectomy and who had not received prophylactic treatment with liver. Twelve had developed macrocytic anemia, and 5 others developed anemia of doubtful nature. The anemias in this series seldom occurred less that two years after operation.

The delay in the onset of megaloblastic anemia is due to the presence in the body of considerable amounts of vitamin B_{12}, most of which is probably available for metabolism. The tissues of a healthy adult may contain from 1000 to 2000γ of vitamin B_{12}.[9] Following total gastrectomy, signs of vitamin B_{12} deficiency do not occur until this reserve has been depleted. There is a variable latent period during which tissue and serum concentrations of the vitamin are falling, but there is still sufficient vitamin B_{12} in the body to prevent the onset of anemia. During this time, the estimation of the vitamin B_{12} content of the serum provides a more accurate index of the state of vitamin B_{12} nutrition. This is illustrated by the following case report.

REPORT OF A CASE

A. E., a 57-year-old Negro woman, had total gastrectomy performed for carcinoma of the stomach in September, 1952. The tissue resected included 1 cm. of distal esophagus and 2 cm. of proximal duodenum. The lesion histologically was an adenocarcinoma, Grade II. The surrounding stomach did not show gastric atrophy. She made a good recovery from the operative procedure and remained in fair health until April, 1954, when there was a rapid spread of abdominal metastases and death in the following month. The only hemo-

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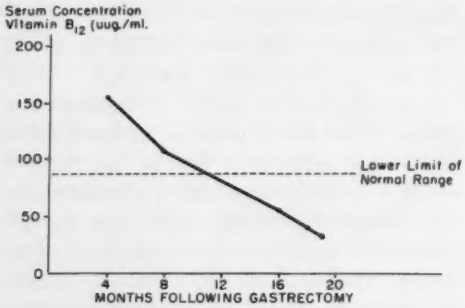
* References 2-4.

† References 5 and 6.

poietic therapy during the 20 months of postoperative observation was given in January, 1953, when she was given a short course of iron by mouth, because blood examination showed a mild iron deficiency anemia. Except for this occasion, blood studies performed at intervals of approximately four months were always normal, the packed cell volume ranging from 40 to 44%. Bone marrow examinations were performed three times during this period, the last occasion being six weeks prior to death. Erythropoiesis was normoblastic in every instance.

Vitamin B_{12} Serum Concentrations.—The technique of vitamin B_{12} serum assay used was that described by Ross.[10] In our laboratory, normal sera show a range of concentration from 86 to 460$\mu\gamma$ per ml., with a mean of 212$\mu\gamma$ per ml. In 16 cases of pernicious anemia in relapse, sera have assayed from 0 to 46$\mu\gamma$ per ml., with a mean of 13$\mu\gamma$ per ml. In the Figure are plotted serial observations on the serum concentration in this patient



Serum concentration of vitamin B_{12}, in micromicrograms per milliliter.

during the greater part of the postoperative period. The first assay, performed four months after surgery, was in the normal range. Eight months after gastrectomy the serum vitamin B_{12} concentration was still in the normal range but was approaching the lower limit of normal. Thereafter, this patient showed subnormal serum concentrations, the last two readings being in the range usually seen in patients with pernicious anemia in relapse.

Absorption of Orally Administered CO^{60} Vitamin B_{12}.—Nineteen months after gastrectomy, when the patient's serum revealed evidence of vitamin B_{12} deficiency, the ability to absorb orally administered vitamin B_{12} was investigated by the test originally described by Schilling.[11] Five-tenths microgram CO^{60} vitamin B_{12} of specific activity 0.21μc per microgram ‡ was administered orally to the patient fasting, followed two hours later by an intramuscular injection of 1000γ of nonradioactive vitamin. The urine was collected over the next 24 hours. Two milliliter aliquots were counted in a well type scintillation counter, and the urinary activity was measured as a percentage of the administered dose. The activity of the 24-hour urine amounted to 3.7% of the administered dose. This is a very low figure and indicates that very little of the radioactive vitamin was absorbed. The test was repeated, the patient being given 100 ml. of neutralized filtered normal gastric juice along with the radioactive vitamin B_{12}. This time urinary activity measured 32% of the administered dose, a figure indicating normal absorption of the oral dose.

‡ Supplied by Dr. Charles Rosenblum, Merck & Company, Inc., Rahway, N. J.

COMMENT

The very small absorption of oral radioactive vitamin B_{12} in patients with total gastrectomy and the improved absorption observed when intrinsic factor is given together with the radioactive vitamin provide additional evidence that the stomach alone secretes intrinsic factor. In the patient reported in this paper, it is reasonable to suppose that inadequate absorption of dietary vitamin B_{12} existed from the time of operation. For more than 18 months, therefore, she was forced to call upon reserve body stores of the vitamin. If a deficiency state is taken to mean a reduction from the optimal body content of a substance, the patient was in a state of vitamin B_{12} deficiency from the time of gastrectomy, even though serum levels were still normal eight months later. During this time, reserve quantities of the vitamin in the liver and other tissues were being utilized. There is evidence that serum has a greater affinity for vitamin B_{12} than has liver tissue [12] and that the body can maintain a normal serum level in the presence of greatly depleted liver reserves. This is a very advantageous mechanism and ensures an adequate supply of vitamin B_{12} to the bone marrow, even in the presence of whole body deficiency.

It is probable that serum vitamin B_{12} concentrations remain low for some time before clinical anemia develops. Mollin and Ross [6] report that, in some patients with pernicious anemia, serum levels may be low for periods of at least one or two years but the blood picture be normal or almost normal. It would have been desirable to have continued ob-

servations on this patient, but she obviously was not going to survive long enough for megaloblastic anemia to develop.

There are practical implications to the observation that vitamin B_{12} deficiency may exist in patients following total gastrectomy, in the absence of megaloblastic anemia. This observation, however, does not necessarily apply to subtotal gastrectomy. Vague symptoms of lassitude, loss of appetite, loss of weight, and general malaise may easily be interpreted as due to metastases, if gastrectomy has been carried out for carcinoma. These symptoms may be a manifestation of vitamin B_{12} deficiency, even in the presence of a normal blood cell count. Prophylactic injections of vitamin B_{12}, as used in the treatment of pernicious anemia, is good practice in patients who have been subjected to this operation.

SUMMARY

Serum vitamin B_{12} concentrations were serially performed on a patient who had undergone total gastrectomy. Values showed a progressive downward trend, and they were subnormal 16 months after the operation. The patient did not develop megaloblastic anemia.

By use of radioactive vitamin B_{12}, difficulty in the absorption of orally administered vitamin was demonstrated.

After total gastrectomy patients should receive regular injections of vitamin B_{12}.

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Carbohydrate Metabolism in Brain Disease

V. Effect of Epinephrine on Intermediary Carbohydrate Metabolism in Schizophrenic and Manic-Depressive Psychoses

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Carbohydrate metabolism is abnormal in patients with manic-depressive, schizophrenic, and involutional psychoses. Fasting concentrations of true blood glucose and whole blood lactic acid are frequently elevated above the normal.[1] The utilization of administered glucose is impaired to some degree in all patients, varying with the clinical status of the patient.[1] Insulin resistance, manifested by a smaller than normal fall in the concentration of blood glucose after the administration of insulin, is also a common finding.* Mobilization of glucose from hepatic glycogen after the administration of epinephrine alone is normal or greater than normal in the psychoses under consideration, except in those patients with malnutrition or psychoses of long duration, where it may be decreased.† However, the mobilization of hepatic glyco-

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* Altschule,[2] p. 139, and Reference 3.

† References 4 and 5 and Altschule,[2] p. 138.

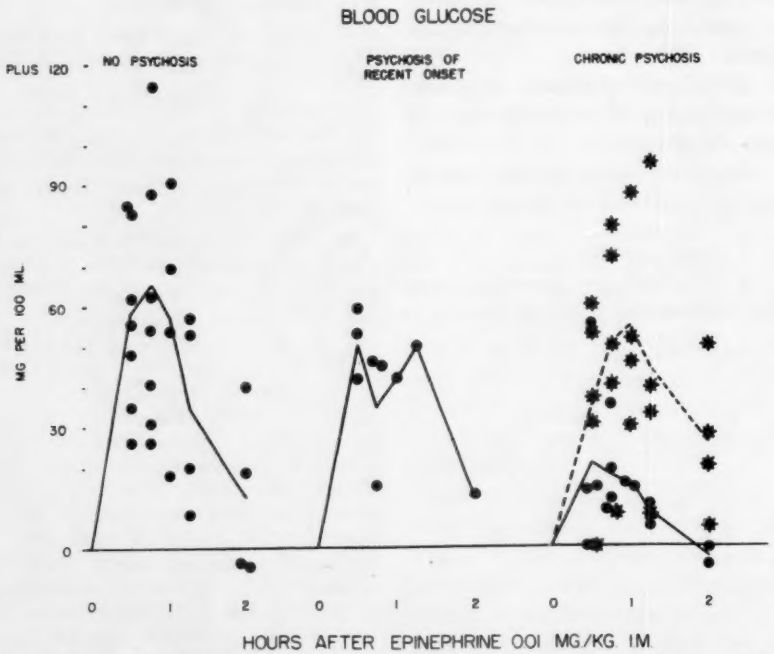

Fig. 1.—Changes in blood glucose level after injection of epinephrine. The crenellated dots refer to patients who had had lobotomy. The lines are averages, the broken lines referring to patients who had had lobotomy.

gen is less than normal in patients with good nutrition and psychoses of recent onset if insulin is administered prior to the administration of epinephrine.[3] Also, blood glucose concentration often shows an abnormal fall from the control level after the administration of phlorhizin; mobilization of glucose temporarily lags behind the excretion of glucose.[6] The fragmentary published evidence that various aspects of carbohydrate mobilization are abnormal in some patients with schizophrenic, manic-depressive, or involutional psychoses stimulated the present study, in which epinephrine was used to mobilize the carbohydrate. In view of the fact that only the blood glucose concentration had been studied in the earlier work,‡ it was decided to study in addition changes in the blood concentrations of lactic, pyruvic, citric, and α-ketoglutaric acids. Lactic acid is of particular interest, since it is called forth from muscle by epinephrine,§ whereas glucose is derived from the liver.[10]

‡ References 1 and 3-6 and Altschule,[2] pp. 138 and 139.

MATERIAL AND METHODS

Observations were made in 6 normal subjects and in 12 patients with psychoses; 4 had psychoses of recent onset, and 8 had chronic psychoses. The ages range from 25 to 50 years. The patients and normal control subjects were of comparable ages. Three of the patients with chronic psychoses had had frontal lobotomies three to nine years previously; at the time of the present study, they were only slightly improved; two of them were still residing in a disturbed ward.

§ References 7-9.

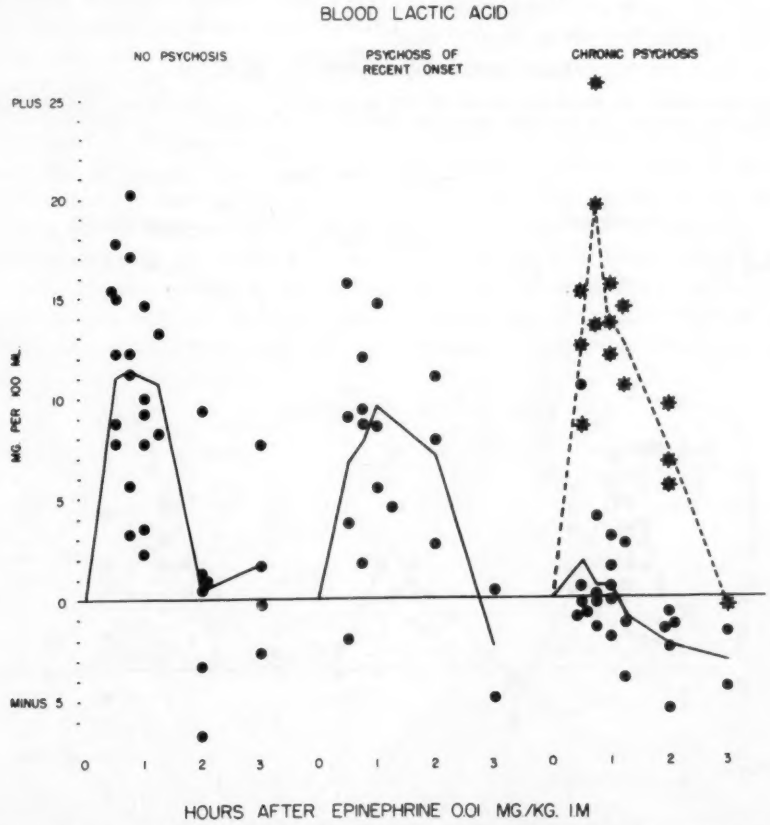

Fig. 2.—Changes in blood lactic acid level after injection of epinephrine. The crenellated dots refer to patients who had had lobotomy. The lines are averages, the broken lines referring to patients who had had lobotomy.

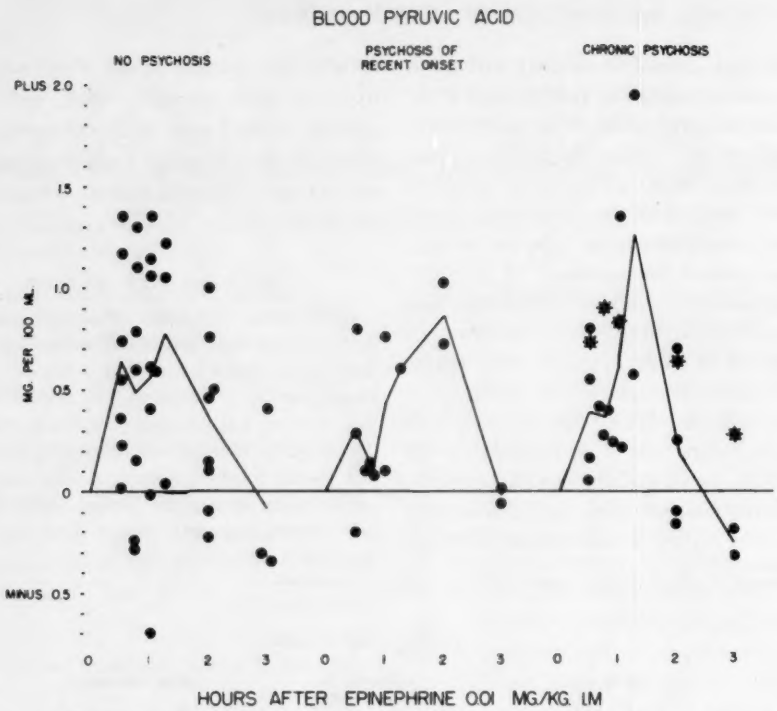

Fig. 3.—Changes in blood pyruvic acid level after injection of epinephrine. The crenellated dots refer to patients who had had lobotomy. The lines are averages.

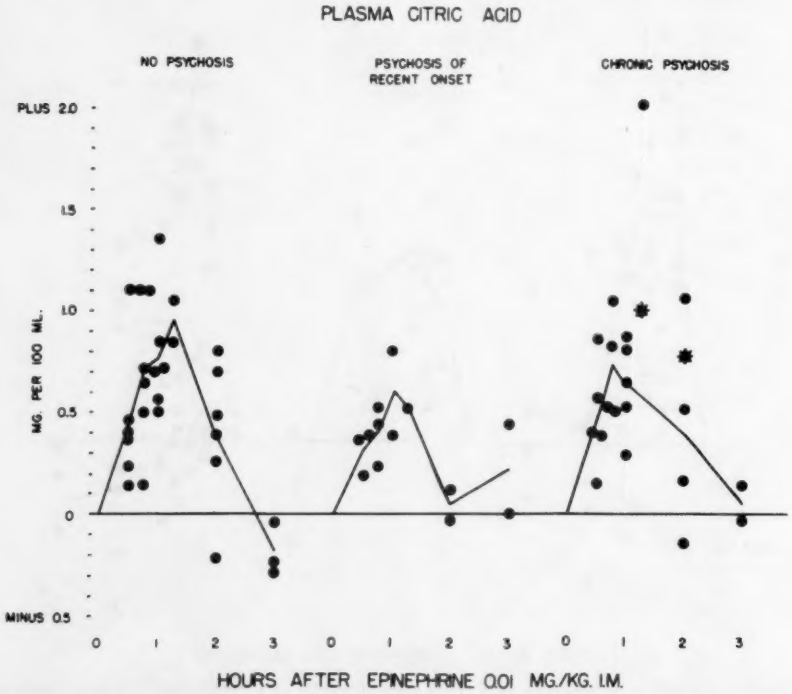

Fig. 4.—Changes in plasma citric acid level after injection of epinephrine. The crenellated dots refer to patients who had had lobotomy. The lines are averages.

Blood concentrations of true glucose and of lactic, pyruvic, citric, and α-ketoglutaric acids were determined; serum inorganic phosphate levels were also followed. The methods used were as previously described.[1] Epinephrine (1:1000, solution Lilly) was injected intramuscularly in a dose of 0.01 mg. per kilogram body weight. All subjects were given a high-carbohydrate diet for three days prior to the test; only well-nourished subjects were used. Blood samples were taken, with previously described precautions, immediately before the injection of epinephrine and one-half, three-quarters, one, two, and three hours thereafter.

OBSERVATIONS

Blood Glucose Concentration.—The blood glucose concentration in normal subjects showed rises after the injection of epinephrine similar to those reported for normal subjects in the literature.[10] The patients with psychoses of recent onset exhibited similar changes (Figs. 1 and 6). Three of the seven patients with chronic psychoses showed less than the normal rise; these patients had not had previous lobotomies. Of the four patients with chronic psychoses who showed normal changes in blood glucose concentration, three had had lobotomies (three to nine years previously). The average maximal rise in blood concentration was 63 mg. per 100 ml. for the six normal subjects, 54 mg. per 100 ml. for the four patients with psychoses of recent onset, 61 mg. per 100 ml. for the three lobotomized patients (five tests) with chronic psychoses, and 26 mg. per 100 ml. for the four unlobotomized patients with chronic psychoses.

Blood Lactic Acid Concentration.—The four patients with psychoses of recent onset showed rises in blood lactic acid level within the range of change found in the six normal subjects and that reported in the literature [11] (Figs. 2 and 6). Four of the eight patients with chronic psychoses showed changes well below this range; these patients had not had previous lobotomies. The three patients with previous lobotomies had normal changes in lactic acid concentrations. The average maximal rises in blood concentrations were 14.3 mg. per 100 ml. in the six normal subjects, 12.7 mg. per 100 ml. in the four patients with psychoses of recent onset, 19.5 mg. per 100 ml. in the three patients with chronic psychoses and previous lobotomies, and 3.6 mg. per 100 ml. in the five patients with chronic psychoses but without previous lobotomy.

Blood Pyruvic Acid Concentrations.—The changes in all groups of subjects were in the same range of change (Figs. 3 and 6). The average maximal change in the blood concentration was 0.92 mg. per 100 ml. in the normal subjects, 0.63 mg. per 100 ml. in the patients with psychoses of recent onset, and 0.98 mg. per 100 ml. in the patients with chronic psychoses. No difference was noted

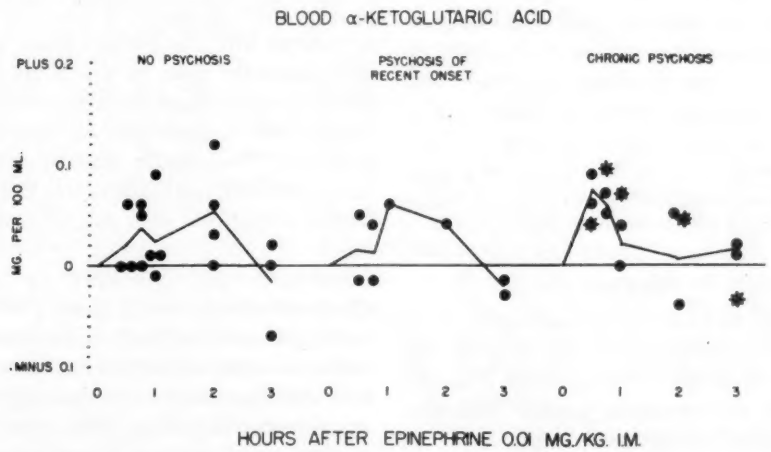

Fig. 5.—Changes in blood α-ketoglutaric acid level after injection of epinephrine. The crenellated dots refer to patients who had had lobotomy. The lines are averages.

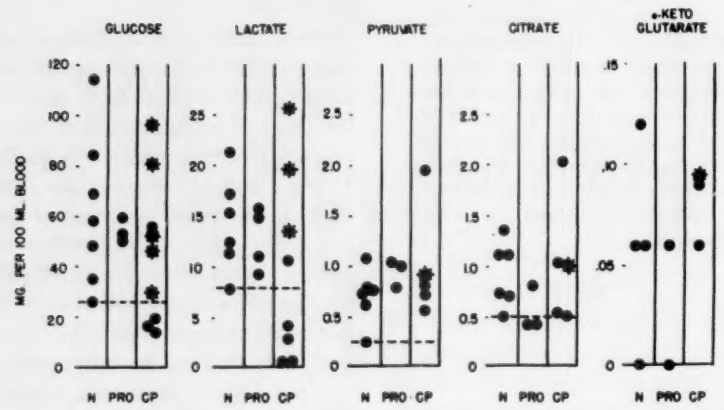

Fig. 6.—Maximal rises in blood constituents after injection of epinephrine. The crenellated dots refer to patients who had had lobotomy.

between the lobotomized and the unlobotomized patients with chronic psychoses.

Plasma Citric Acid Concentration.—The changes in all three groups of subjects were in the previously described normal [12] range. The average maximal changes in plasma citric acid concentration after the injection of epinephrine were 0.84 mg. per 100 ml. plasma in the normal subjects, 0.53 mg. per 100 ml. in the patients with psychoses of recent onset, and 1.02 mg. per 100 ml. in the patients with chronic psychoses (Figs. 4 and 6). No differences were noted between those with and those without previous lobotomy.

Blood α-Ketoglutaric Acid Concentration.—In the nine studies on blood α-ketoglutaric acid level, the intramuscular injection of epinephrine induced a rise in the blood concentration in all but two cases; these two showed no significant change. The range of change in all three groups of subjects was the same (Figs. 5 and 6).

COMMENT

The rise in blood sugar concentration following the intramuscular injection of epinephrine in patients with psychoses is usually described as normal or greater than normal ‖; these studies were largely made on patients with psychoses of recent onset and measured total reducing substance rather than true blood glucose. It has been well established that the injection of epinephrine raises the blood reduced-glutathione concentration to a significant degree not related to changes in blood volume.¶ As in glucose-tolerance tests,[16] the interpretation of blood glucose changes following administered epinephrine should be based on true glucose determinations. Measurements of the blood glucose concentration made in the present study show that hepatic glycogenolysis after a single injection of epinephrine is normal in patients with psychoses of recent onset and in patients with chronic psychoses who had had lobotomies three to nine years prior to the test; other patients with chronic psychoses showed diminution in hepatic glycogenolysis. These results confirm and extend earlier observations made in this laboratory,[4] largely on patients with psychoses of recent onset.

Holmgren and Wohlfahrt [5] reported an abnormally large rise in blood glucose concentration after multiple injections of epinephrine in patients with mental disease. The later injections of the hormone perhaps induced increased rises in blood sugar because of a greater than normal conversion to gly-

‖ References 4 and 5 and Altschule,[2] p. 138.

¶ References 13-15.

cogen of the lactic acid liberated from skeletal muscles by the earlier injections in each series of injections of epinephrine.

Freeman and co-workers,[3] on the other hand, reported that the rise in blood glucose concentration observed in psychotic patients after the administration of epinephrine was less than normal if the epinephrine was preceded by the administration of insulin. This abnormality occurred in the same patients who manifested a smaller than normal fall in blood glucose concentration after the administration of insulin alone. Freeman's observations [3] suggest that in patients with mental disease there is resistance not only to the blood glucose-lowering effect of insulin but also to the hepatic glycogen-forming effect of insulin. The seeming discrepancy between the work of Freeman and co-workers [3] and that of Holmgren and Wohlfahrt [5] is perhaps explained by the evidence that the glycogen deposited in the liver by the action of insulin is derived from glucose, while that formed under the influence of epinephrine is from lactic acid.[17]

The data reported here show that the changes in blood concentration of lactic acid after a single injection of epinephrine are normal in patients with psychosis of recent onset and in the patients with chronic psychoses who had had a previous lobotomy. The patients with chronic psychoses but without lobotomy three to nine years earlier showed a decreased rise in lactic acid level suggesting (*a*) an increased rate of formation of hepatic glycogen from the mobilized lactic acid, (*b*) decreased mobilization of lactic acid from the muscles, or (*c*) both. These patients also showed a decreased rise in blood glucose. Cori and co-workers [18] have demonstrated in animals a close correlation between the glucose and lactic acid changes, and we have made the same observation in patients here. The decreased rise in glucose and lactic acid concentration observed in the patients with chronic psychoses who had not had a lobotomy was not due to debility or to a low-carbohydrate diet; all subjects were given a high-carbohydrate diet for three to five days before each test, and were well-nourished to begin with.

The data of the present study show normal changes in blood concentrations of pyruvic, citric, and α-ketoglutaric acids after the injection of epinephrine. There appears to be no direct relation between changes in blood levels of glucose and lactic acid, on one hand, and of these other substances on the other.

Apparently, the citric acid formed after the injection of epinephrine is metabolized normally. This is in contrast to the abnormal utilization of citric acid formed after the administration of glucose [1] or the injection of insulin.[19] No explanation for this difference suggests itself.

The abnormality in carbohydrate mobilization revealed when phlorhizin is injected in psychotic patients [6] cannot be correlated with abnormalities in the response to epinephrine; presumably the mechanisms involved in the two phenomena are not the same.

The decreased rises in blood glucose and lactic acid concentrations observed in patients with chronic psychoses who had not had lobotomies are not specific: Similar abnormalities have been observed in patients with chronic debilitating diseases,[11] head injuries,[20] diabetes mellitus,[11] and idiopathic epilepsy.[21] The reversal of the abnormal findings in patients with chronic psychoses three to nine years after frontal lobotomy cannot be explained. The fact that the psychosis persisted, whereas this biochemical change did not, emphasizes the nonspecificity of the latter with respect to mental disease.

SUMMARY AND CONCLUSIONS

The carbohydrate metabolism after injection of epinephrine in doses of 0.01 mg/kg. body weight was studied in normal subjects, in patients with psychoses of recent onset, and in patients with chronic psychoses with and without previous lobotomy. The psychoses were schizophrenia and manic-depressive psychoses.

The change in blood pyruvic, citric, and α-ketoglutaric acid concentrations were the same in all three groups of subjects. Rises in

true blood glucose and lactic acid concentrations were normal in patients with psychoses of recent onset but were decreased in those patients with chronic psychoses who had not been lobotomized.

The decreased rise in blood glucose and lactic acid concentrations after the injection of epinephrine is not specific; it is observed in a variety of chronic diseases. The relation of the observations reported here to other abnormalities observed in patients with psychoses is discussed.

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Treatment in Internal Medicine

MANAGEMENT OF SYSTEMIC ARTERIAL HYPERTENSION

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DIAGNOSIS

IN A DISCUSSION of the management of arterial hypertensive disease no topic is of greater importance than proper diagnosis. Despite the fact that we do not find distinguishing characteristics for most of our patients with hypertension, the considerable prognostic and at times therapeutic value of making an etiologic diagnosis renders careful diagnostic study highly desirable. This discussion is directed mainly toward treatment of those patients who have (1) so-called "essential" hypertension or (2) hypertension from known etiologic factors but whose elevated blood pressure fails to respond to causal therapy.

We believe that in order to arrive at the correct diagnosis it is desirable to have a complete history and physical examination (including blood pressure in both arms and in one thigh), roentgenograms of the heart and lungs in three or four projections, a 12-lead electrocardiogram, estimation of basal blood pressure after heavy sedation, fractional phenolsulfonphthalein test, blood urea nitrogen concentration, intravenous pyelogram, and a pharmacologic test (preferably with phentolamine [Regitine]) for pheochromocytoma in a majority of patients. With slightest suspicion of possible kidney disease, and in all hypertensive patients under 25 years of age, urine cultures should be made. More extensive studies of the urinary system are done when indicated (because of our special interest, a relatively high percentage of our patients have estimates of their ability to clear the plasma of inulin and *p*-aminohippurate, as well as other special renal-function studies). Patients suspected of having pheochromocytoma have urinary catechols measured,[1] in addition to several drug tests, glucose-tolerance test, and observations on temperature, heart rate, and arterial pressure fluctuations.

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The Renal Laboratory is supported by the Youngstown (Ohio) Area Heart Association of the American Heart Association, the National Heart Institute, the Iowa State Department of Health, and the State University of Iowa.

CLASSIFICATION

Once an attempt has been made to categorize the disorder, we believe the next reasonable step in the treatment of the hypertensive person is an attempt to grade objectively the severity of the cardiovascular abnormality. This affords the physician a means by which he may follow the progress of the disease, recognize more easily improvement or deterioration, and relate his own experience to that of others within the limits of human judgment in order to arrive at the best possible appraisal of the patient's progress. We classify each patient on each visit to the office or hospital according to the scheme depicted in Table 1, assigning a numerical grade under each of six column headings. Initially the grading system is used to help answer the question of how the patient's hypertension should be managed, and later to indicate observable results of therapy.

SELECTION OF PATIENTS AND OF THERAPY

Since there is no agreement as to the natural history of hypertensive disease, a controversy exists as to whether and how many of these patients should be treated. Some believe that even Grade I hypertensives may benefit significantly from vigorous ther-

apy, as with sympathectomy [2] or a fairly strict drug regimen. Recognizing the incomplete information that we have on life history, the majority of writers in this field seem to believe that surgery and the stricter medical programs should be used for treatment only when definite evidence of cardiovascular damage from the hypertensive process has appeared (such as advanced Grade II or Grade III).

Chiefly because of our experience with treatment of patients with malignant hypertension, where regression of severe signs of symptoms and signs of complications of hypertension are relieved by this approach.

Some help concerning the specific questions of which patient should be treated, when, and in what manner can be gained from published reports of three large series of hypertensives.* In general, these reports bear out the clinical impression that many persons with arterial hypertension live comfortable and productive lives untreated. For instance, Bechgaard found that 71% of patients with hypertensive cardiovascular disease survive at least 12 to 20 years after

TABLE 1.—*Classification of Hypertension*

Grade*	Retina		Kidney	Brain	Heart	Basal Diastolic Blood Pressure, Mm. Hg
	Arteriosclerotic Changes	Hypertensive Changes				
I	Normal, or mild thickening of arterial wall	Normal, or sparse focal constriction	Normal by urinalysis, PSP, and urea clearance	Normal	Normal, or slightly increased thrust of left ventricle	90-100
II	Moderate arterial wall thickening	Generalized narrowing and frequent focal constriction	PSP or PAH plasma clearance slightly depressed, but urea clearance normal; proteinuria (trace); slight increase in hyaline and epithelial casts	Normal, or evidence of one stroke	Above, plus left ventricular hypertrophy, myocardial infarction, or angina pectoris	102-110
III	Above changes plus arteriovenous compression and "copper" or "silver wire" light reflex	Above changes plus hemorrhages or soft or hard exudates	50% reduction in PSP or PAH clearance; less severe but pronounced fall of urea clearance and GFR; maximal specific gravity not >1.020; mild proteinuria	Evidence of two or more strokes	Any of the above changes plus congestive heart failure	112-130
IV	Above changes plus venous thrombosis or arterial obliteration	Retinal or papillary edema, with or without above changes	Hematuria; moderate proteinuria; uremia; PSP, PAH clearance, GFR, and urea clearance very low; fixed specific gravity	Hypertensive encephalopathy, with or without evidence of stroke	Intensification of above findings	Above 130

* Grade is determined by adding changes in various compartments and dividing by six. When the resultant figure is a fraction, the assigned grade is placed at the next higher or lower figure, depending on whether hypertensive eyeground changes and/or diastolic blood pressure grades are higher or lower, greater weight being given these elements of the system. Example: Retinal arteriosclerotic changes 2, hypertensive changes 3, kidney 2, brain 2, heart 2, blood pressure 3=total 14÷6=2.3. Final grade, III.

hypertensive disease is the rule following hypotensive therapy, we have come to doubt the easy explanation that hypertension represents a compensatory reaction which serves to maintain flow of blood through narrowed vessels. Rather, we suspect that "hypertension may beget hypertension" and that therapy directed toward moderation of blood pressure may alter the course of hypertensive disease, either directly through alleviation of cardiovascular strain or indirectly through some presently unrecognized metabolic improvement. There can be little doubt that onset and that over one-half of the total remained in good health for that period. However, the data clearly show that certain groups have bad prognoses. For instance, hypertension is a serious threat to life in the young hypertensive man but definitely less of a threat to the young hypertensive woman, not so serious a threat to life in the middle-aged, and frequently a mere annoyance in the elderly. In addition, our own clinical experience has made us appreciate the ob-

* References 4-6.

servation that when a patient changes from one classification group to a higher one the prognosis untreated is likely to be poor. There is widespread agreement that the untreated malignant or Grade IV hypertensive seldom lives more than 12 months.[3]

Thus, we believe that therapy should be most vigorous in those patients with malignant hypertension and in severe Grade III hypertensives. We watch the young man with hypertension with some concern and institute active therapy at the first definite evidence of progression of the vascular disease. The majority of the remaining hypertensive patients are treated in a manner which will allow them maximum relief of symptoms on the simplest possible regimen. They are observed at intervals appropriate to the severity of their hypertensive state and prognosis, with the understanding that any new development may alter our plan of therapy. It is in this group of patients that we have the least practical data concerning prognosis. For this reason our view is that rewards of vigorous treatment may be small, that life span and happiness may not be increased by therapy, and that the meticulous regimen necessary for complete abolition of the hypertension may be far worse than the relatively mild disease. Here again, except in the very old and arteriosclerotic patient, evidence of progression or the appearance of complications may alter our approach and philosophy drastically.

WEIGHT REDUCTION

Starvation regularly causes lowering of arterial pressure in normotensive persons. Many obese persons have erroneously high blood pressure readings due to artifacts related to the compression of the adipose tissue in sphygmomanometric observations. Both of these are reasons partially responsible for the widespread but erroneous belief that reduction of weight routinely will lower blood pressure and cause remission of symptoms in obese hypertensive patients. However, sometimes a good effect on hypertensive disease, which seems greater than that ascribable to reduction of the extra heart work imposed by the extended vascular network, will be seen after simple weight reduction in the order of 10% to 20%. Morover, it is well documented that there is an inverse relationship between obesity and longevity, whether the cause of death in the obese be cardiovascular or otherwise. For these reasons, we recommend that all our obese hypertensive patients reduce moderately and gradually.

PSYCHOTHERAPY

Of the devices in this field available to the nonpsychiatrist, reassurance and explanation are most important in treatment of hypertensive patients. Persons with essential hypertension are often tense, restless, and emotionally labile persons, whole symptoms become worse with progression of this disease.† Associated with these symptoms are wide swings of blood pressure. Often these patients can be made more relaxed and less apprehensive about life in general and their disease in particular by means of slightly mitigated and unemotional discussion of their problems. Indeed, this type of therapy supplemented by barbiturates or Rauwolfia preparations is all that we use in treatment of most persons with Grade I and many patients with Grade II essential hypertension while we observe the course and estimate the progress of the disease. In our experience, more elaborate methods of psychotherapy, including analysis, are not practical methods of controlling the majority of patients with essential arterial hypertension.

DIETARY SODIUM RESTRICTION

Although low-salt diets were advocated in this country as a therapeutic measure in hypertension as early as 1922,[8] very little use was made of this knowledge until Kempner [9] advocated a rice-fruit diet in 1944. Critical analyses of the effects of this diet ‡—which furnishes 2000 calories, 15 to 20 gm. of protein, 4 to 6 gm. of fat, and 100 to 150 mg. of sodium daily—reveal that the major reduction in blood pressure which occurs when the

† References 3 and 7.

‡ References 10-12.

diet is fed hypertensive patients is due to the low sodium content. Evidence is available which suggests that a more liberal selection of food may be allowed than with the rice-fruit diet if the sodium content is maintained below 200 mg. per day. Such rigid restriction of sodium will lower the blood pressure in one-third to one-half of the patients who will accept it for a period of two months. The unpalatability of such a diet, however; poor patient acceptance, and occasional untoward results in patients with severe renal disease render the diet a difficult one to administer. Unless the physician has great interest, confidence, and knowledge about low-salt diets, it is very difficult to persuade many hypertensives to remain on the program. If dietary sodium restriction is contemplated, it is most important for the physician to determine the plasma carbon dioxide content or alkaline reserve (combining power) and the blood urea, urea nitrogen, or nonprotein nitrogen, in order to avoid the threat of producing a potentially serious low-sodium syndrome in his patient.

We have used low-sodium diets when other programs have failed in Grade III and IV hypertensives. We also have seen additive effects when this program of salt restriction has been combined with drug therapy programs or when drugs have been added to the low-salt program. Our chief difficulty has been in convincing our patients, especially the more urbane ones, that such drastic dietary measures were necessary. Finally, we have used the rice-fruit diet as an inexpensive form of therapy for impecunious patients, since the necessary ingredients can be procured at reasonable cost. A gratifying long-term good response to low-salt dietary therapy is illustrated by the following case report:

A 52-year-old man was seen in June, 1950, complaining of exertional chest pain and morning occipital headaches. Physical examination revealed basal blood pressure readings of 210/120, which had been known to exist for at least two years. Hemorrhages, exudates, and severe focal constrictions were seen in the ocular fundi. There was palpably increased left ventricular activity, left ventricular hypertrophy by electrocardiogram, urinary specific gravity of 1.020 after dehydration, and 2+ proteinuria.

During a general discussion of treatment the patient manifested an interest in the rice-fruit diet. He was placed on this regimen, and the blood-pressure fell to 170/100 in two weeks and to 150/80 in four weeks. The angina became less troublesome, and the retinopathy and proteinuria cleared. Improvement continued after protein and extra fat were added to the diet. For the past four and one-half years the patient has continued to follow his low-salt schedule. The only times that his blood pressure has exceeded 160/90 have been on the two occasions, both of about two weeks' duration, when salt was used freely at our request. During the entire period of therapy the patient has worked as a stockroom clerk, with only rare chest pain (none during the past year), and no headache. The retinopathy has cleared completely, as has the proteinuria. The patient's only complaint now is of expected fatigue in very hot weather.

RAUWOLFIA SERPENTINA

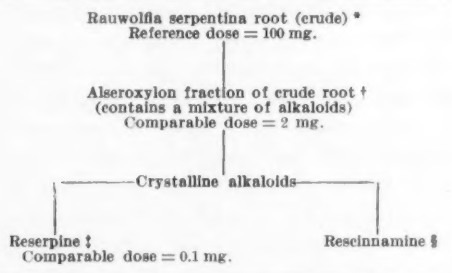
Rauwolfia and its alkaloids were introduced into American medicine in 1951 by Wilkins, Judson, and Stanton,[13] and since that time they have gained wide acceptance as tranquilizing agents with hypotensive qualities. Several recent papers § have summarized their use in the treatment of human arterial hypertension. Many preparations of rauwolfia are available now to the physician. Table 2 summarizes the relationship of the various preparations to the whole root. The chief pharmacologic effect of all of these substances (except rescinnamine,‖ which has little hypotensive effect) is to decrease peripheral arteriolar resistance, lower blood pressure, and produce bradycardia. There is little effect after chronic administration on cardiac output, renal blood flow, or glomerular filtration rate.[17] The calming effect seems to be the result of the drug's action in the midbrain, where it appears to have a certain "adrenergic blocking" influence.[18] This is manifested clinically by nasal congestion and bradycardia and possibly by the reduc-

§ References 14-16.

‖ Kirkendall, W. M.; Anderson, G. A., and Lubin, R. I.: Comparison of Hypotensive and Renal Vascular Effects of Derivatives of Rauwolfia Serpentina in Man: Alseroxylon and Rescinnamine, unpublished data.

tion of the arterial pressure. Some other effects of rauwolfia are increased motility of the bowel, possibly an increase in gastric acid production, and a tendency toward weight gain. The tranquilizing effect of rauwolfia is not associated with narcosis but does promote sleep, a feeling of relaxation, and a diminution in anxiety and compulsiveness. At times patients complain of nightmares or vivid dreams, and depressed states have been reported after long-continued therapy.[18] With a crude root dosage of 100 mg., or alseroxylon fraction dosage of 2 mg., or reserpine dosage of 0.1 mg., given one to four times a day, it may take one to six weeks for full effects of the drug to appear. It is also apparent that many effects of the drug do not disappear immediately after cessation of administration but may take up to three weeks to be lost. Rauwolfia preparations have few or no severe toxic properties in the usual dose ranges and have a wide margin of safety; for example, a 20-month-old child ingested 260 mg. of reserpine at one time without serious aftermath.[19]

TABLE 2.—*Rauwolfia Serpentina and Its Derivatives*


Rauwolfia serpentina root (crude) *
Reference dose = 100 mg.
Alseroxylon fraction of crude root †
(contains a mixture of alkaloids)
Comparable dose = 2 mg.
Crystalline alkaloids
Reserpine ‡
Comparable dose = 0.1 mg.
Rescinnamine §

* Commercial preparation: Raudixin, E. R. Squibb & Sons, New York.
† Commercial preparation: Rauwiloid, Riker Laboratories, Inc., Los Angeles.
‡ Commercial preparations: Serpasil, Ciba Pharmaceutical Products, Inc., Summit, N. J.; Serpiloid, Riker Laboratories, Inc.; Reserpoid, The Upjohn Company, Kalamazoo, Mich.; Rau-Sed, E. R. Squibb & Sons; Crystoserpine, Smith-Dorsey, Division of The Wander Company, Lincoln, Neb.; Sandril, Eli Lilly & Company, Indianapolis.
§ Not commercially available; manufactured by Riker Laboratories, Inc.

The hypotensive effect, tranquilizing action, and low toxicity of rauwolfia qualify this drug as one which should be considered in the treatment of all types of hypertensive patients. We agree with Wilkins[16] that one of its chief uses should be in Grade I or II labile psychoneurotic hypertensives with tachycardia and many complaints. When used alone in this group, it may be expected to benefit at least 50% of patients. In addition, we have used the drug frequently as an adjunctive agent with veratrum, hydralazine, or methonium drugs in both dual and multiple combinations. It has been our experience, in common with others,¶ that such schedules are additive and perhaps synergistic in accomplishing a blood pressure decline in many instances. Despite the difficulty of being certain of such things, it also appears that some of the effects of rauwolfia tend to offset objectionable characteristics of the more powerful antihypertensive drugs.

HYDRALAZINE

Hydralazine (1-hydrazinophthalazine) is a hypotensive drug whose exact mode of action is obscure. It probably suppresses the outflow of sympathetic vasopressor impulses from the midbrain,# but it may inhibit a cerebral vasopressor substance[25] and it also may have a peripheral vascular site of action.[26] When given intravenously, the drug has profound cardiovascular effects, causing tachycardia and increased cardiac output,[23] renal blood flow,[27] and liver blood flow,[28] with decreased vascular resistance in the entire splanchnic bed and in the cerebral circuit.[29] These effects are not maintained in significant degree during chronic administration, although tachycardia does persist unless counteracted by a bradycrotic drug such as veratrum or rauwolfia. Hydralazine has been used widely in combination with other hypotensive drugs and alone. Opinions of its value when used alone for treating clinical arterial hypertension have varied,* but most writers have found it a useful adjunctive agent for combined therapy with other drugs, chiefly of the methonium class.†

Despite an orderly schedule of drug administration and considerable patience, it has

¶ References 16 and 20-22.
# References 23 and 24.
* References 30 and 31.
† References 16, 32, and 33.

been our experience that side-effects and lack of long-term control of hypertension in most patients make hydralazine alone an impractical drug for prolonged therapy of hypertension. It has been a valuable combining drug when used with methonium preparations and rauwolfia. We have demonstrated repeatedly that hydralazine will cause equivalent blood pressure reduction in smaller doses and with fewer side-effects when used in such combinations. At the present time hydralazine is used in place of rauwolfia preparations in treatment of Grade II hypertensive patients if rauwolfia side-effects are intolerable (a rare circumstance). We use hydralazine with rauwolfia in those Grade II hypertensives who do not have a satisfactory response to the latter drug alone. We substitute hydralazine for rauwolfia in combined treatment of Grade III or IV patients with methonium drugs when results with the first combination are not satisfactory or if lethargy, depression, weight gain, nasal stuffiness, or diarrhea seriously hinders the patient's progress. When hydralazine is used in combination with methonium drugs we have given the drug between methonium injections in two or three doses. We seldom have used more than 500 mg. a day in combined therapy and have seen no instance of the syndrome resembling lupus erythematosus.[34] Arthralgia and mild edema have been common during the use of hydralazine, but these have merely a nuisance quality and always are reversible when the drug is discontinued.

VERATRUM PREPARATIONS

Veratrum preparations, derived from roots and rhizomes of Veratrum album and Veratrum viride, have the capacity to lower blood pressure and to produce bradycardia and respiratory slowing. Often seen with these effects are nausea and vomiting and, occasionally, severe postural hypotension. The site and mechanism of action of these drugs is not entirely understood. Hoobler[35] believes that their action is the result of ability to produce an after-discharge in afferent nerves from the carotid sinus and coronary artery receptors after each normal discharge. Green[36] discusses other data concerning the pharmacology of veratrum drugs.

Newer preparations of veratrum alkaloids do not vary so much in composition from batch to batch as did original extracts, but they do produce similar hemodynamic effects, as well as causing troublesome nausea. Among the veratrum drugs with constant composition and reproducible effect are those from Veratrum viride (alkavervir [Veriloid] and Vergitryl) and protoveratrines A and B (Veralba and Provell Maleate) from Veratrum album.

Because blood pressure reduction with veratrum preparations is intermittent and frequently causes nausea in full doses, many workers have curtailed their use sharply as primary treatment for hypertension. In certain situations these drugs may be of great value to the hypertensive patient, particularly in treatment of hypertensive crises, for which intravenous veratrum has proved extremely valuable. Wilkins[16] has recommended its use in combination with other hypotensive agents, where he obtains a therapeutic effect with veratrum below emetic doses. Since the advent of rauwolfia as a more suitable bradycrotic drug, we have almost discontinued the use of veratrum except in the treatment of hypertensive encephalopathy, preeclampsia, and eclampsia.

GANGLIONIC BLOCKING DRUGS

Of the large group of drugs which have as their main action interruption of neural transmission at synapses of both the sympathetic and parasympathetic nerves, hexamethonium bromide or chloride and pentapyrrolidin bitartrate (pentolinium; Ansolysen) are the most commonly used preparations. Extensive reviews of the pharmacology and methods of management of hypertensives with these drugs are available.‡ Space does not allow detailed discussion of these matters here. In general, therapy with the two agents is similar; both may be given by mouth or parenterally; both have the same side-effects qualitatively, and results seem to be similar.

‡ References 33, 37, and 38.

Smirk [37] has presented data which indicate that pentapyrrolidin is active for longer periods of time (possibly two hours) than hexamethonium given by the same route, but this has not been accepted universally. The effective dose of pentapyrrolidin is much smaller than that of hexamethonium, the ratios between the two being approximately 1:8 for oral and 1:5 for subcutaneous routes. In our experience treatment with oral pentapyrrolidin has been more satisfactory than with oral hexamethonium. This we have attributed to the smaller dose necessary for control and to the longer duration of effect. Most of our experience, however, has been with parenteral methonium therapy—a method of administration which is predictable, relatively simple, and with few gastrointestinal side-effects.

The chief action of these drugs in hypertensive patients is to lessen arteriolar and venous tone by sympathetic paresis, with resultant pooling of blood in dependent regions. Hence, although blood pressure can be lowered in the supine position with large doses, little effect often is seen on blood pressure in the recumbent patient, although he may develop pronounced arterial hypotension when standing motionless. This characteristic effect results in blood pressure reduction which is most marked at the time of the peak action of the drug and with the patient in the upright position. There may be no blood pressure reduction five to eight hours after a dose and only a modest fall when the patient is supine, even at the peak of the drug's effect. Such uneven control of blood pressure would seem to be justified by the fact that vascular damage from hypertensive disease can be reduced by methonium salts even when given only two or three times a day. Moreover, there probably is an advantage in combating a potentially damaging excessive rise in arterial pressure when the patient is up and about and likely to be most active. Nevertheless, most writers agree that it is desirable also to lower resting blood pressure to some degree throughout the day in severely ill hypertensives. For this purpose hydralazine, a short-acting agent, is given between methonium doses,[38] or rauwolfia, a long-acting drug, is given daily for long-term "background" control.[39] Veratrum preparations combined with methonium drugs, either with or without rauwolfia, have failed to give us results comparable with the effects of hydralazine so combined. We have had no extensive experience with other agents combined with methonium drugs.

Methonium drugs have frequent undesirable side-effects, all secondary to autonomic blockade, the more important ones being profound postural hypotension, hypotonia of gastrointestinal and vesical musculature, blurring of vision, dryness of the mouth, and impotence. These can be controlled satisfactorily by adjustment of methonium dosage and the judicious use of neostigmine (Prostigmin), bethanechol (Urecholine), or pilocarpine as indicated (often for not more than two weeks). Because the difference between the effective dose of methonium preparations and one which causes undesirable hypotension is very small (being as little as 10 mg. of oral and 2 mg. of parenteral preparations) each patient's problem must be individualized. The strict clinical supervision that is required for adequate control makes the use of this drug a very expensive one from the standpoint of the patient's and his physician's time.

Because of the amount of time involved, the patient cooperation required, and our doubt as to the benefit to mild hypertensives, it is our practice to use methonium preparations (always now with hydralazine or rauwolfia or both) only for Grade III and IV hypertension. Our program always is started in the hospital, usually with subcutaneous hexamethonium two or three times a day with an adjunctive drug or drugs. Contrary to the practice of others,[39] we start most of our patients on a restricted sodium diet in order to enhance the effect of the methonium drugs. Blood pressure levels are observed closely while the methonium dosage is raised rapidly. By the end of two weeks our patients are ready to leave the hospital with full knowledge of their drugs, their actions, and the methods of counteracting undesirable

side-effects. We do not have patients measure their own blood pressure routinely. Instead, we advise them to stand motionless for two minutes at the time of peak drug action (which we have determined in the hospital). If there is weakness or slight faintness which disappears immediately with activity, we feel that we are at or near proper dosage levels; if the patient is very faint or feels no effect, we readjust dosage after observation in the office or out-patient clinic. We attempt to see our patients once a week during the first month out of the hospital, and we find that this interval can be extended rapidly as time goes on. In addition to the usual admonitions concerning regular bowel habits for those on oral therapy, we advise our patients to avoid exercise in a hot atmosphere, to drink alcoholic beverages cautiously if at all, to avoid large doses of vasodilating drugs such as nicotinic acid, and to reduce their dosage of methonium drugs during intercurrent illness (especially fevers), for we have had hypotensive accidents in all of these situations.

Duration of life has been increased considerably in severe, particularly malignant, hypertension with the methonium drugs in combination with hydralazine and rauwolfia in our hands. Compared with a similar group of patients with malignant hypertension treated with a variety of other methods, including low-salt diets, pyrogenic agents, thoracolumbar sympathectomy, veratrum preparations, and other drugs, methonium-treated patients have survived longer, had fewer complications, lost the signs of malignant hypertension sooner, and, we believe, felt much better. Such methonium regimens, however, have not altered the course of occasional very rapidly deteriorating malignant hypertensive patients or those who had far-advanced renal failure when first seen. We do use methonium programs for those hypertensives who have uremia but whose renal failure is not progressing rapidly.

OTHER DRUGS

No other drug approach to treatment of hypertension has enjoyed the success and acceptance of those mentioned above. There are many other drugs used for special problems of hypertensives and many others which have been advocated as antihypertensive agents but which, because of disagreeable side-effects, development of tolerance, or relative ineffectiveness, have not been accepted generally.

The adrenergic blocking agents (Dibenzyline,§ Dibenamine,‖ and Ilidar ¶) have the property of attaching themselves to receptor areas which are activated by the sympathetic nervous system or by circulating adrenergic substances and, thus, prevent adrenergic mediators from having access to receptor end-organs.[36] Uniformly this group of drugs causes a high incidence of side-effects such as severe postural hypotension, nasal stuffiness, headache, nausea and vomiting, abdominal distress, and occasionally drug fever. Drug tolerance develops rapidly in most patients, while large doses almost invariably cause unpleasant symptoms. We seldom use these drugs for hypertensive therapy at this time.

Some physicians use and advocate potassium thiocyanate for relief of hypertensive headache.[40] However, partially because of the necessity for meticulous control of blood levels of thiocyanate in chronic treatment and partly because of its relatively feeble and unpredictable hypotensive response, thiocyanate is not widely used as a hypotensive agent today. The mechanism of action of this drug is not known.

Hydergine is a mixture of equal parts of dihydroergocornine, dihydroergokryptine, and dihydroergocristine, all derivatives of ergotoxine. These dihydrogenated ergot alkaloids have the property of relaxing smooth muscle and dilating blood vessels. Some favorable clinical reports of the effect of Hydergine on hypertension have appeared,[41] but, in general, the drug has been found to

§ N - phenoxyisopropyl-N-benzyl-β-chloroethylamine hydrochloride.

‖ N,N-dibenzyl-β-chloroethylamine hydrochloride.

¶ 6-allyl-6,7 dihydro-5H-dibenz(c,e)azepine phosphate.

be of limited value,[42] especially when used orally or sublingually. Our experience with dihydrogenated ergot alkaloids and Hydergine has indicated a very narrow, often imperceptible margin between the therapeutic and toxic dose when given subcutaneously. We have found little or no effect on the blood pressure of 10 patients with established essential hypertension when Hydergine was given sublingually in doses up to 3 mg. daily. We do not believe that this interesting group of drugs has much to offer at this time in therapy of hypertension.

SURGICAL TREATMENT

Surgery for arterial hypertension traditionally has implied some type of sympathetic nerve path interruption. Recently several workers # have removed the entire adrenal gland bilaterally with or without sympathectomy in an attempt to control severe hypertensive disease. It is far too early to evaluate this new approach thoroughly, but some initial successes have been noted which warrant continuation of the investigation.

Sympathectomy for hypertension has not been employed so often since the advent of the methonium drugs, which are capable of producing complete but reversible sympathetic interruption by means of total autonomic ganglionic blockade. The surgical procedure, however, is a practical and at times a worthwhile method of lowering blood pressure, especially when the patient is sitting or standing, and of delaying the progress of hypertensive cardiovascular disease. There is much difference of opinion concerning the extent and the utility of the procedure, the method of selection of patients for it, and the age at which it should be done.[46] Smithwick has presented data which indicate that thoracolumbar sympathectomy prolongs life in Group II, III, and IV hypertensives unless renal failure is advanced.[2] Physiological studies on his patients * have demonstrated significant cardiovascular effects after sympathectomy—such as abolition of reflex arteriopressor peaks—which may be as important in extending life as primary reduction of blood pressure. It has been demonstrated repeatedly that sympathectomy of any type improves the response of patients to hypotensive drug and dietary therapy.

We have continued to employ thoracolumbar sympathectomy for certain of our hypertensive patients. Chief among these are those of Grade III or IV severity who are too irresponsible or unintelligent to manage a personal program of methonium therapy. We also tend to recommend sympathectomy to very young Grade III or IV hypertensives, feeling that their chronic problem may be made simpler and less expensive and perhaps safer by having such an irreversible surgical measure employed early in their clinical course. Because we have had unfortunate results with sympathectomy in patients with severe arteriosclerosis, we avoid this approach in such patients and in elderly persons whose life expectancy probably does not justify such a painful and formidable type of treatment. Our single absolute contraindication to sympathectomy in arterial hypertension is progressive renal insufficiency.

SPECIAL PROBLEMS IN TREATMENT OF ARTERIAL HYPERTENSION

A. Encephalopathy. — This neurological complication is seen chiefly in severe hypertension, during bouts of acute glomerulonephritis, in eclamptic patients, and occasionally as an acute development in persons with pheochromocytoma. Modern antihypertensive drugs, if used properly, are far superior to older methods of magnesium sulfate or hypertonic glucose or sucrose administration, previously used in treating this complication. Except for the encephalopathy of pheochromocytoma, which should be treated by adrenergic blockade with phentolamine (Regitine) or piperoxan (Benodaine), and eclampsia, in which methonium drugs should not be used because of danger to the fetus,[49] individual preference seems to dictate choice of the antihypertensive agent. Corcoran, Dustan, Taylor, and Page[40] have com-

References 43-45.

* References 47 and 48.

mented on the effectiveness and economy of a controlled intravenous infusion of sodium nitroprusside for encephalopathy, while others have documented the efficacy of purified veratrum preparations † and methonium drugs ‡ used intravenously in these acute emergencies. We have used hydralazine intravenously in treatment of acute hypertensive encephalopathy in eight patients, all of whom did well after therapy was instituted. We used 15 to 25 mg. of hydralazine intravenously every one to two hours, depending on blood pressure response, and changed to intramuscular or oral therapy as soon as possible. We also have used intravenous alkaverir (Veriloid) and a preparation of the ester alkaloid fraction of veratrum viride (Vergitryl) for this purpose and have found them to be entirely satisfactory.

B. Cerebral Vascular Accidents.—There is a question whether (1) an untreated hypertensive patient who has just had a cerebral accident should be treated or (2), if already under antihypertensive treatment, he should have it continued during the acute period of the stroke. These are problems which cannot be answered with finality at this time. Theory would suggest that blood pressure lowering would be beneficial in a person suffering from acute cerebral hemorrhage, probably not beneficial in one who has had acute cerebral thrombosis. We have attempted to treat hypertensive patients with cerebral vascular accidents in accord with this reasoning, using parenteral hexamethonium in the acute stage in doses sufficient to lower the blood pressure if hemorrhage is suspected. Our data on the results of such a program are meager, but others [40] have been favorably impressed with such an approach.

When hypertensive patients are seen some time after the acute cerebral vascular injury, we avoid starting vigorous antihypertensive therapy (if indicated) for at least 6 to 10 weeks after the stroke, chiefly in order that collateral vessel formation not be endangered. Many hypertensives with strokes, particularly the severely arteriosclerotic ones, are not treated with the more active hypotensive agents unless they have pressing complications.

C. Congestive Heart Failure.—When this complication is primarily due to hypertension, treatment with hypotensive agents can be most gratifying. As peripheral resistance is lowered, cardiac work is diminished. Results of the lessened load soon become apparent in relief of breathlessness, diminution in cardiac size, improvement in the electrocardiographic tracing, and amelioration of angina. At times, congestive heart failure is corrected without addition of digitalis or desalting regimens. If digitalis is used during the initial treatment of congestive heart failure, it is our practice to discontinue its use as soon as significant hypotension has been achieved (usually within one month). Usually digitalis has not had to be restarted.

Hydralazine, which increases cardiac work acutely and which may increase anginal pain or precipitate failure, should be used with caution in the presence of cardiac complications. Adrenergic blocking agents, such as Dibenzyline, also may produce tachycardia, increase cardiac work, and cause angina. Their use should be avoided in patients with congestive heart failure and angina pectoris if possible. The other hypotensive drugs discussed seem to have no adverse effect on the heart or heart failure unless severe hypotension is produced.

D. Uremia.—This complication indicates a very poor prognosis in the hypertensive patient. This is particularly true if azotemia is rapidly progressing, for many therapeutic possibilities are contraindicated under such conditions. If uremia is mild and not progressive, we attempt to effect a gradual but definite depression of the usually high diastolic pressure by using hydralazine, veratrum, methonium salts, or low-sodium diets, alone or in combinations, but avoiding, if possible, further increase in blood urea nitro-

† References 35 and 50.

‡ References 32 and 40.

gen. A significant percentage of patients in this category (perhaps one-third) will have reduction of plasma nonprotein nitrogen to normal levels. Others will have no change in their blood chemistry values despite reduction of pressure but will continue to do well over fairly long periods (we have three patients with essential hypertension who have had blood urea nitrogen levels of between 35 and 50 mg. per 100 ml. for three to four years, yet are working regularly).

The patients who do not do well on the above programs and those who have rapidly increasing urea retention tax the physician's resourcefulness. Methonium drugs accumulate in the body and become unpredictable, surgery of all forms is distinctly contraindicated, low-sodium diets often accentuate body sodium deficits due to "salt losing nephritis," and other hypotensive drugs are usually ineffective. Pyrogen therapy in our hands has been of no benefit to these patients. Our only practical approach has been to offer these patients a diet high in fat and carbohydrates, similar to that advocated by Borst to stop endogenous protein catabolism. Unfortunately, owing to nausea and vomiting from the uremia, this diet seldom is effective for long periods in ameliorating this state.

E. Expense.—After the supply of samples from pharmaceutical houses is exhausted, there comes a time when the hypertensive patient is confronted with the fact that he has an expensive disease. Not only does he find that the drugs cost a considerable sum, but he frequently finds that he has to buy both a sphygmomanometer and a considerable amount of time from his physician so that the drugs will have their proper effect. Although the situation changes with each new effective measure, we have been impressed that our therapy in the nonindigent hypertensive patient has frequently been tempered by the consideration of cost to the patient. It is not unusual for patients on elaborate programs to spend more than $50.00 per month for drugs alone. For this reason as well as others, we evaluate periodically and critically the effectiveness of each drug in each program, particularly in those plans in which several drugs are used. This has meant frequent removal of a drug from an established program for a period of time long enough to demonstrate its usefulness or permanent removal if it is found to be of no value. We have thus removed many drugs from what appeared to be optimal programs without damage, stopped the ingestion of potentially harmful drugs, continued to reevaluate combined drug therapy for hypertension, and, last but not least, reduced considerably the cost of hypertensive therapy to the patient.

SUMMARY

The treatment of hypertension should be undertaken only after the most accurate diagnosis and classification possible. Therapy should be graded to the severity of the disease or to the seriousness of the prognosis. For milder forms of essential hypertension, reassurance, explanation, and weight reduction, with or without rauwolfia or sedatives, are frequently effective. For control of more advanced grades of essential hypertension Grades III and IV) methonium salts usually in combination with rauwolfia or hydralazine are the programs of choice. Other methods of treatment and some special problems of the management of systemic arterial hypertension are discussed.

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Case Reports

MYXOMA OF LEFT ATRIUM SIMULATING MITRAL STENOSIS

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and
ZHUEIR A. MALHAS, M.D., Chicago

PRIMARY tumors of the heart are rare, slightly more than 300 cases having been reported in the literature. Intra-atrial myxoma is the commonest, constituting approximately 50% of all cases reported. Of these, 75% are said to occur in the left atrium. This tumor has varied clinical manifestations. It is one of the lesions that may simulate mitral valvular stenosis.* Recent advances in the technique for cardiac operation make successful therapy theoretically possible. Therefore, today the early clinical recognition of such tumors is of great practical significance. In five cases recorded before 1954, the clinical diagnosis was made prior to death.† In three of these angiocardiography revealed a constant filling defect of the left atrium ‡ and a surgical exploration was performed. In two an attempt at removal of the tumor was unsuccessful and both patients died. The fourth case was accidentally found in a patient surgically explored for mitral commissurotomy.[5] The mitral valve was normal, and the patient died after an attempt at extirpation of the tumor. In the fifth case diagnosis was made from the clinical history and changing cardiac murmurs.[4] However, death occurred suddenly, before operation was possible. The case reported in this paper illustrates the similarity between the clinical signs and symptoms of intra-atrial tumors and rheumatic mitral stenosis and emphasizes the importance of correct diagnosis for operative treatment.

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* References 1, 2, 6, and 7.

† References 3-5 and 8.

‡ References 3 and 8.

REPORT OF A CASE

The patient was a 40-year-old white woman, admitted to Wesley Memorial Hospital on Nov. 26, 1952, for mitral commissurotomy. The patient had been apparently well until six months previously, when she noted dyspnea and ankle edema. She was treated with the usual measures for cardiac failure and stopped working. Despite this management and bed rest, she again developed ankle edema two weeks prior to hospitalization.

Past history was negative for migratory arthritis, chorea, and rheumatic fever. However, the patient had had frequent sore throats, the last one four months before the onset of the present illness. The family history was noncontributory. Physical examination revealed an emaciated white woman with markedly swollen legs. The temperature and respirations were normal. The blood pressure was 100/56, and pulse rate, 94 per minute. The patient weighed 46 kilograms. The lungs were clear. The apical impulse of the heart was felt in the fourth intercostal space 8 cm. from the midsternal line. Palpation revealed a systolic apical thrill. Auscultation revealed a harsh blowing Grade IV systolic murmur at the mitral area. There was a Grade I diastolic murmur in the anterior axillary line. Pulmonic second sound was greater than aortic second sound. One examiner described a short, sharp presystolic accentuation merging into the systolic murmur. The liver was tender and palpable 1 fingerbreadth below the right costal margin. There was 4+ pitting edema of both legs. The reflexes were normal.

Laboratory Examination.—The hemogram was normal. The leucocyte count was 15,750. The differential count was normal. The sedimentation rate was 10.5 mm/hr. Urinalysis was negative except for 30 mg. of albumin per 100 cc. Serum sodium, potassium, chloride, CO_2-combining power, and nonprotein nitrogen were normal. The Kahn test was negative. Roentgen examination revealed marked right ventricular enlargement and moderate enlargement of the left atrium and main pulmonary artery (Fig.

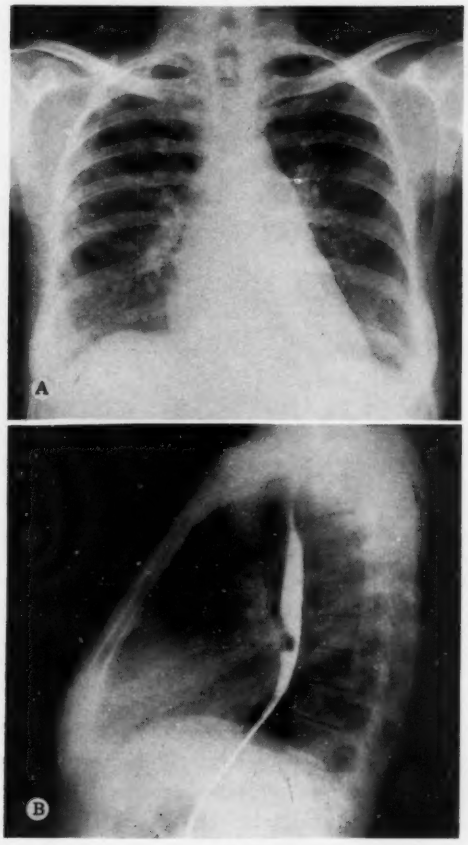


Fig. 1.—*A*, x-ray of chest in posteroanterior projection, showing prominence of pulmonary artery and passive congestion of lungs; *B*, x-ray of chest in lateral projection, showing left atrial and right ventricular enlargement.

1). The electrocardiogram indicated right ventricular hypertrophy and strain, pulsus mitralis, and digitalis effect.

Hospital Course.—The patient was treated with digitoxin, ammonium chloride, meralluride, U. S. P., (Mercuhydrin), carbacrylamine resins (Carbo-Resin), and low-sodium diet. She responded well and lost 8 kilograms. On the 31st hospital day the patient was taken to the operating room for mitral commissurotomy. She was anesthetized with oxygen and ether. The blood pressure at the beginning of the procedure was 92/80. When the patient was turned to the right lateral position, she became cyanotic and the blood pressure was unobtainable. With levarterenol (Levophed) the blood pressure rose to a satisfactory level, and the chest was opened. The left lung appeared normal. The left auricular appendage was normal but slightly thickened. A finger was introduced into the left atrium, and the mitral valve was felt to be soft and pliable, without evidence of regurgitation or stenosis. The cardiac action then became feeble, and the electrocardiogram showed idioventricular rhythm with a 3:1 auriculoventricular block. The chest was then closed. When the patient was turned on her back, the cardiac rhythm, rate, and blood pressure were better. However, the patient remained unconscious and died eight hours after the operation.

Autopsy Findings (No. 3425, by Z. A. Malhas).—Autopsy revealed tumor of the left atrium, cardiac hypertrophy of the right ventricle, hypoplasia of right coronary artery, healed infarct of left ventricular myocardium, tumor emboli to renal and left middle cerebral artery, and recent infarcts in brain and kidneys.

The heart, which weighed 340 gm., had a dilated and hypertrophied right ventricle. Within the left atrium there was a pedunculated, polypoid, soft gelatinous tumor measuring 3.5 cm. in greatest diameter (Figs. 2 and 3) arising from the posterior angle of the foramen ovale. The pedicle measured 0.8 cm. in diameter. When the heart was held in the vertical position, the tumor dropped into the left ventricle for a distance of 2 cm.; when the heart was held horizontally, the tumor fell backwards and partially obstructed the pulmonary veins. The heart

Fig. 2.—Tumor of left atrium in situ. Note glistening gelatinous appearance.

valves were all normal. The myocardium was grossly normal except for an old infarct of the posterior wall of the left ventricle. The infarct had a maximum measurement of 3.5 cm. The coronary arteries were normal except for marked hypoplasia of the right coronary artery and slight arteriosclerosis. The left artery was not unusually large.

Microscopically the tumor was composed of small papillary projections covered by flattened endothelium continuous with the endothelial lining of the left atrium (Figs. 4 and 5). The central portion of the tumor was composed of myxomatous tissue with a small number of spindle-shaped and stellate cells and a moderate number of multinucleated cells.

Fig. 3.—Tumor of left atrium partially sectioned. Note proximity to mitral valve.

There were focal areas of recent hemorrhage and scattered lymphocytes, plasma cells, and pigmented macrophages. At the base of the tumor there were gland-like structures partly or completely lined by nonciliated mucin-producing columnar epithelium (Fig. 5).

Examination of the brain revealed occlusion of the left middle cerebral artery by a myxomatous tumor thrombus. A recent area of infarction involved the frontal and temporal lobes on the left side in the region of the internal capsule. Similar tumor

Fig. 4.—Photomicrograph of tumor, showing myxomatous character; reduced approximately ⅔ from mag. × 66.5.

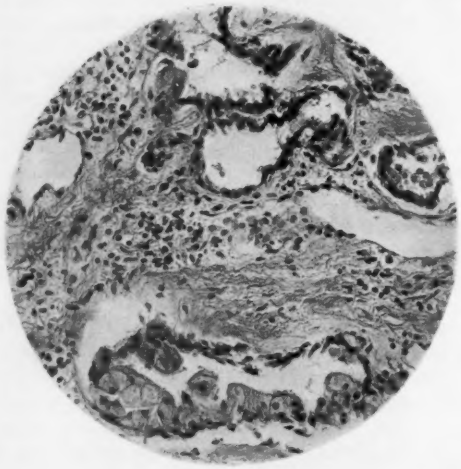
thrombi were present in many interlobular arteries of the kidneys, with areas of recent infarction in both.

COMMENT

In retrospect several features of this case deserve comment.

1. The rapid and relentless cardiac failure in spite of accepted treatment and restricted activity in a short period of time is not characteristic of rheumatic heart disease.

Fig. 5.—Photomicrograph of section from base of tumor, showing epithelial lined grandular structures; reduced approximately ⅔ from mag. × 150.



This is also considered diagnostically significant in most other cases of cardiac tumor reported in the literature.

2. The cardiac configurations and electrocardiographic changes were like those of mitral stenosis. The comparable changes were the result of obstruction of the mitral orifice by tumor.

3. Systolic and diastolic murmurs, like those of rheumatic mitral stenosis and insufficiency, were constantly present. These observations differ from other reported cases in which the changing murmurs were helpful in the diagnosis of cardiac tumors. In the case reported in this paper, the fact that a portion of the tumor extended through the mitral orifice may account for the consistency of the murmurs.

4. The autopsy finding of multiple "tumor emboli" in the brain and kidneys is of particular interest. It serves as another point of similarity to embolic phenomena of subacute bacterial endocarditis based on a rheumatic valvulitis.

5. It is also worthy of note that at time of operation a sudden change in the patient's position precipitated cyanosis. It is furthermore important to realize that myxomatous tumors may be soft and gelatinous and thus difficult or impossible to palpate at the time of operation.

SUMMARY

A case of myxoma of the left atrium simulating mitral stenosis is presented. The single most significant diagnostic fact is the relentless cardiac failure developing in a short time, albeit other diagnostic features would warrant a diagnosis of rheumatic mitral disease. Sudden changes in position in patients with polypoid intracardiac tumors may aggravate clinical signs and symptoms. This was noted in this case at time of operation. When cardiac tumors are suspected, it is recommended that changes of position be utilized as part of the examination as well as angiocardiographic visualization of the heart chambers.

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AMYLOID NEPHROSIS SECONDARY TO HODGKIN'S DISEASE

Report of a Case

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SECONDARY amyloidosis, as a complication of Hodgkin's disease, has been described as being unusual to rare in occurrence.* In a survey of the literature from 1832 to 1949, Wallace and co-workers,[3] reviewed approximately 40 cases in which amyloidosis developed and described a case of their own. Since 1949, additional cases have been described.†

We should like to report a case in which the clinical picture was that of a nephrotic syndrome with uremia, whose etiology could not be determined but which proved to be amyloidosis, secondary to clinically unrecognized Hodgkin's disease.

REPORT OF CASE

A 37-year-old white man entered the hospital with a history of being in good health until four months previously. At this time he noted progressive anorexia and asthenia. One month prior to admission, he developed edema of the lower extremities and intermittent edema of the eyelids. Two weeks later he noted the onset of 10 to 12 loose, watery stools daily, which were occasionally blood-streaked. He had no associated abdominal pains, chills, fever, or vomiting, but he did have hiccoughs.

There was no previous history of renal disease. The patient had continued to work as a mechanic in military service, until the day of hospital admission.

Physical examination on admission revealed a markedly pale, lethargic, edematous white man. B. P., 127/70; pulse rate, 96; temperature, 98.6 F orally. Conjunctiva were pale, and funduscopic examination revealed Grade I retinopathy bilaterally. The lungs were clear, and there were no cardiac abnormalities. The abdomen appeared distended and was tympanitic to percussion, but no fluid wave was elicited. Bowel sounds were hypoactive. No organs or masses could be palpated, but the abdominal muscles were tense. There was no superficial lymphadenopathy. A 4+ pitting edema of the lower extremities was noted, as well as presacral edema.

During the hospital stay, the patient showed persistent albuminuria, hematuria, anemia, hypotension, electrolyte imbalance, and hypoproteinemia. The hospital course was that of a progressive renal insufficiency, terminating in uremia, and death occurred in 23 days. The anasarca persisted in spite of attempts at diuresis, with regulation of fluid intake, human serum albumin, blood, and electrolytic solutions. The daily urine output rapidly decreased from 1000 cc. on admission to 75 cc. at time of death.

Laboratory studies revealed a microcytic, hypochromic anemia with hemoglobin values ranging from 11.6 gm. to 9.1 gm. RBC varied between 3,600,000 and 2,030,000. All urine specimens showed 4+ albuminuria. Amyloidosis secondary to multiple myeloma was considered; but Congo red dye was not available. Bence-Jones proteinuria was lacking, and sternal aspiration was negative. The NPN increased from initial value of 168 mg. per 100 cc. to 345 mg. at death. Creatinine averaged 3.5 mg. per 100 cc. Total protein initially was 4.15 gm., with albumin 1.5 gm. and globulin 2.65 gm. Terminally, a total protein of 3.4 gm. with albumin 1.85 gm. and globulin 1.55 gm. was found. Sodium levels were between 123 and 135 mEq/L.; potassium varied from 4.3 to 6.1 mEq/L. Chlorides were 80 to 104 mg. per 100 cc., and CO_2-combining power varied from 13.4 to 22 mEq/L. X-ray of the chest was normal. Stool cultures were negative.

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* References 1 and 2.

† References 4 and 5.

Fig. 1.—Photograph of the kidney to illustrate the diffuse enlargement. The organ weighed 500 gm.

Fig. 2.—The cut surface of the kidney demonstrates the marked thickening of the cortex.

Necropsy Findings.—External examination of the body revealed marked edema of both lower extremities and presacral area. A hard movable nodule measuring 3 cm. in diameter was felt in the right supraclavicular area. No other superficial lymphadenopathy was evident. There was 200 cc. of a clear serous fluid in each pleural cavity, and an estimated 300 cc. of a similar fluid in the peritoneal cavity. The lungs were edematous, with multiple patchy areas of consolidation. The heart

Fig. 3.—Photomicrograph of the spleen illustrating replacement of the Malpighian corpuscle with amyloid. Hematoxylin and eosin; × 60.

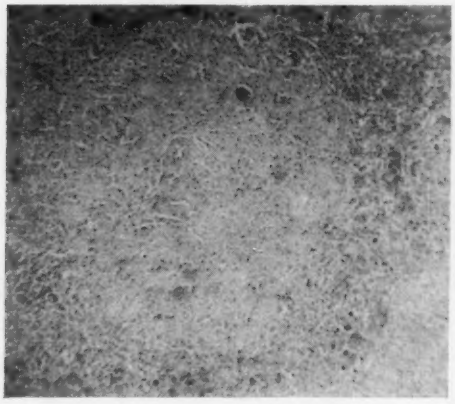
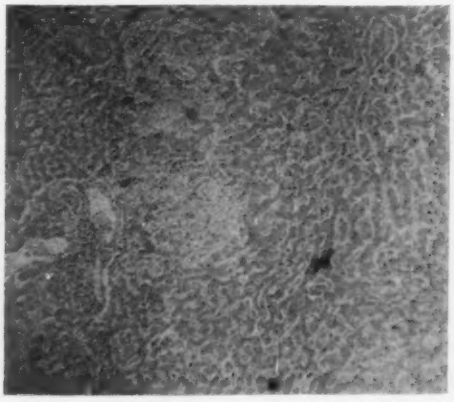


Fig. 4.—Low-power view of the liver showing compression atrophy of liver cells by amyloid deposits. Hematoxylin and eosin; × 60.



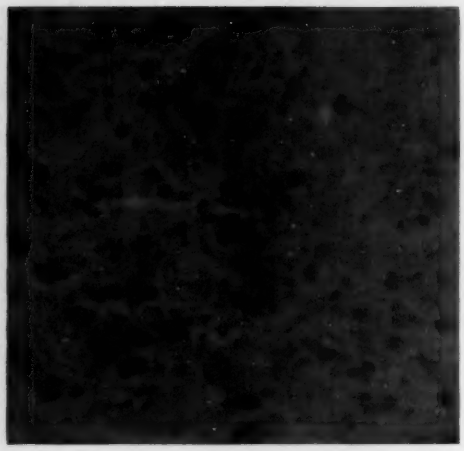
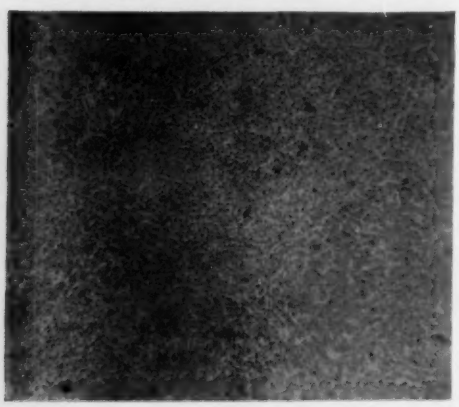


Fig. 5.—High-power view of the liver shown in Figure 4. Hematoxylin and eosin; reduced slightly from mag. × 430.

was not remarkable. The liver weighed 2000 gm. but was otherwise normal on gross inspection. The spleen weighed 400 gm., and the cut surface was markedly congested, but the Malpighian corpuscles were accentuated in areas, giving it a sago-like appearance. The kidneys were markedly enlarged, weighing 500 gm. each. The surface was smooth after decapsulation. Both kidneys were swollen. The cortices measured 1.5 cm. in thickness. The cut surface had a glossy, moist appearance throughout. Numerous lymph nodes were isolated deep in the right supraclavicular area. These ranged in diameter from 3 cm., the largest, to 1 cm., the smallest. These were discrete, and the cut surface revealed a fish-flesh appearance. There was no mediastinal lymphadenopathy, but there was involvement of the retroperitoneal lymph nodes in the region of the pancreas.

Fig. 6.—Low-power view of the liver illustrating an area of involvement with Hodgkin's disease. The large hyperchromatic nuclei seen in the center are Dorothy Reed cells. Hematoxylin and eosin; × 60.



Histological examination of the lymph nodes in the supraclavicular and retroperitoneal areas revealed complete displacement of the normal architecture with amyloid deposits which gave a positive Congo-red reaction. Numerous lymphocytes, plasma cells, eosinophiles, and Dorothy Reed cells filled the space not occupied by the amyloid.

The spleen contained numerous amyloid deposits, which in many areas replaced the Malpighian corpuscles. The splenic sinuses were filled with numerous Dorothy Reed cells, eosinophiles, lymphocytes, and plasma cells.

The liver sections revealed multiple areas where the normal liver parenchyma was replaced by numerous giant cells of the Dorothy Reed type. In addition, numerous amyloid deposits were seen between the hepatic cords and the reticuloendothelial lining of the hepatic sinuses.

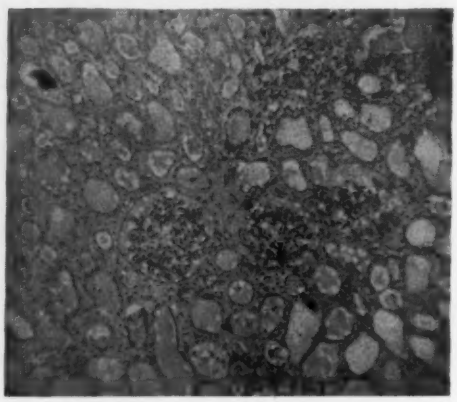


Fig. 7.—Photomicrograph of the kidney showing four glomeruli with amyloid deposits and severe tubular nephrosis. Congo red stain; × 60.

The kidney sections were typical of a severe amyloid nephrosis. The glomeruli were partially replaced with amyloid, there being no evidence of proliferative glomerulitis. The tubules were uniformly distended with eosinophilic casts. There were definite degenerative and regenerative changes in the renal tubular epithelium.

SUMMARY AND CONCLUSIONS

In a century of medical literature (1849-1949), about 40 cases of amyloidosis secondary to Hodgkin's Disease were reported. Since 1949, additional cases have been described.

In this case, the picture presented was that of a nephrotic syndrome, secondary to extensive renal amyloidosis. Hodgkin's disease affecting supraclavicular and periaortic lymph nodes, liver, and spleen was discovered after death. The actual cause of death was considered to be amyloid nephrosis.

Hodgkin's disease, as such, did not appear symptomatic clinically and was important primarily as it related to the amyloidosis.

In the differential diagnosis of nephrotic syndrome, when etiology is obscure, hypertension is absent, urinary findings are scant aside from albuminuria, and the disease is progressive, Hodgkin's disease complicated by renal amyloidosis should be considered.

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MASSIVE RESECTION OF SMALL AND LARGE INTESTINE

Report of Case with Survival

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R. B. WILSON, M.D.
and
C. G. McEACHERN, M.D., Fort Wayne, Ind.

WHEN a surgeon performs laparotomy and encounters gangrenous intestine, resection of the dead segment must be carried out if the patient is to have any chance for survival. It is of interest to report the following case of a 57-year-old man, from whom almost the entire small bowel and a portion of the large intestine were removed because of gangrene due to mesenteric artery thrombosis. He has survived, in fair health, for 23 months, with only the stomach, duodenum, 8 in. (20 cm.) of jejunum, and that portion of the large intestine distal to the midtransverse colon.

REPORT OF CASE

The patient, a 57-year-old Negro man, was in good health until three days prior to admission to the Methodist Hospital in Fort Wayne, Ind., on Jan. 26, 1953. His illness began after an evening of excessive indulgence in alcoholic beverages. The following day he noted generalized abdominal pain, constipation, nausea, and vomiting. These symptoms continued with increasing severity for three days. He then sought medical aid.

During the previous year, he had been treated for a duodenal ulcer and this had responded promptly to medical therapy. A system review was not remarkable; nor was anything of importance obtained in the family history. One of his brothers and one of his sons were physicians.

Upon admission, he was moderately dehydrated, the temperature being 98 F orally; the pulse, 100 per minute, and the respirations, 24 per minute. The heart was regular and free of murmurs. The physical findings of significance were confined to the abdomen. Distension of the abdomen was moderate, and tenderness to deep palpation was present in all quadrants. In the epigastrium there was marked rebound tenderness. No masses were palpable nor was shifting dullness in evidence. Peristalsis was absent. A scout film of the abdomen disclosed a normal gas pattern. An upright film failed to disclose free air beneath the diaphragm. The leucocytes numbered 14,000, with a marked shift to the left. The hemoglobin was 14.5 gm. The urinalysis disclosed some granular casts and a faint trace of albumin. A serum amylase determination was within normal limits.

A Wangensteen tube was inserted into the stomach, with recovery of copious quantities of dark, fecal-like material. After 3 liters of such material were obtained, and after dehydration had been corrected by the administration of intravenous fluids, surgery was undertaken. It was our impression that this man was suffering from a generalized peritonitis, possibly due to a slowly leaking perforated duodenal ulcer.

With the patient under general anesthesia, on Jan. 29, 1954, the abdomen was entered through a vertical right midrectus incision. A most foul odor issued from the abdominal cavity. There was approximately 200 cc. of blood-tinged fluid in the peritoneal cavity, and the entire small bowel from 8 in. distal to the ligament of Treitz appeared necrotic, black, and friable. Above that point, there was a sharp change in color and the proximal 8 in. of jejunum appeared viable. The entire colon was stained dark, but when several small vessels were incised in the region of the midtransverse colon free bleeding was obtained. Resection of all except the proximal 8 in. of jejunum, the entire ileum, the ascending colon, and the proximal half of the transverse colon was carried out. An end-to-end anastomosis was made between the jejunum and transverse colon, with a two layer anastomosis of 00 chromic absorbable surgical (gut) sutures. The patient withstood the surgical procedure without difficulty.

The postoperative period was marked by a troublesome diarrhea of 10 to 12 liquid movements per day, necessitating the administration of large quantities of intravenous fluids with suitable electrolytes, including rather large quantities of potassium. The serum electrolytes were maintained near nor-

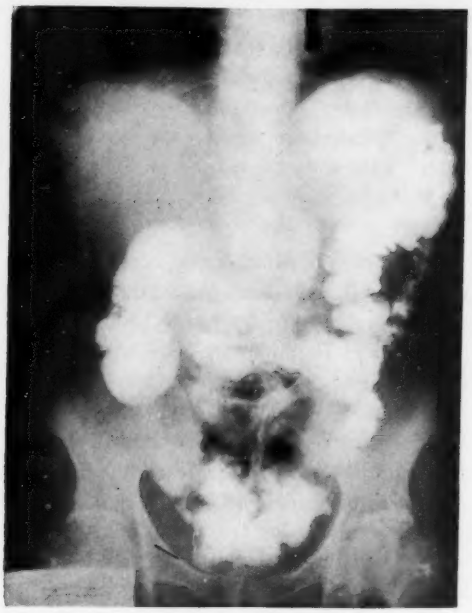

Fig. 1.—Almost complete absence of small intestine.

mal levels at all times. Frequent feedings of small quantities of food high in caloric value and low in fat content were instituted. Numerous drugs, including methantheline (Banthine), camphorated opium tincture (paregoric), and belladonna compounds did not decrease the diarrhea.

The wound healed per primum. He was dismissed from the hospital on Feb. 15, 1953, 20 days after surgery. Because of the continuing diarrhea, administration of a liter of intravenous fluids was carried out daily for about three weeks after his release from the hospital. There then gradually was noted a decrease in frequency of bowel movements.

His weight, which was 160 lb. (72 kg.) prior to surgery, had fallen to 145 lb. (65.25 kg.) at the time of dismissal from the hospital. It gradually decreased to 125 lb. (56.25 kg.), where it has since stabilized.

Fig. 2.—Resected specimen, consisting of entire jejunum, ileum, and ascending and half of transverse colon.

His plasma proteins at dismissal were 7.4 gm. per 100 cc., with a normal albumin-globulin ratio. The hemoglobin was 15 mg. three months after surgery. A barium meal three months after surgery disclosed the very short portion of the intestinal tract remaining (Fig. 1). The passage of barium seemed most rapid. It was thought that there might be some compensatory hypertrophy of the remaining small intestine.

His bowel movements now have decreased to five per day, and he has abandoned the frequent meals and confines his food intake to four home-cooked meals daily. He notes some weakness but generally feels quite well. He takes no medication and does not use supplementary vitamins. It has not been possible to obtain comprehensive blood chemistry determinations or metabolic studies of food utilization, for he feels too well and will not submit to these studies. He works every day, managing his small restaurant.

Pathology Report.—The pathologist examined the resected specimen after it had been well fixed in formalin.

"The gross specimen consists of a resected length of bowel, at one end of which is the proximal portion of the jejunum and the other end, the middle portion of the transverse colon. The entire mass of bowel is very foul smelling and the surface is covered by a reddish gray exudate. In the mesentery of the jejunum, there are identified a number of small blood vessels which appear to be completely filled by thrombus. The bowel wall throughout, is dark red and obviously gangrenous. The jejunum and ileum vary from 3 to 7 cm. in diameter. The cecum is 8 cm. in diameter. The ascending colon and transverse colon are 8 cm. in diameter. Opening of the bowel reveals the mucosa throughout its length to be diffusely infiltrated with blood and there is obvious necrosis of the mucosa of the bowel. The jejunum and ileum measure 14 feet in length. The cecum, ascending, and transverse colon measure 26 inches in length. All measurements were taken following formalin fixation.

"Microscopic sections of the mesentery of the jejunum reveal fatty tissue with several small thrombosed arteries in the fat. Sections of the jejunum, ileum, and the colon present extensive gangrene of the bowel with almost complete loss of mucosa. There is a thick fibrinopurulent exudate on the serosa."

The diagnoses were (1) extensive resection of jejunum, ileum, cecum, ascending, and transverse colon; (2) mesenteric artery thrombosis; (3) extensive gangrene of the bowel; (4) acute peritonitis.

Doerfler, in 1917,* resected all of the small intestine but the duodenum and 1 ft.

* Doerfler, cited by Wangensteen, O. H. in Christopher,[1] p. 1067.

of jejunum. When his patient was alive in 1923, he was prompted to ask whether man might live without the small intestine. There are no reports, to our knowledge, of one surviving in good health without a portion of the jejunum.

Marien and McCorriston,[2] in 1952, reviewed the literature of cases undergoing massive resection and found a number of cases that had survived for a period sufficiently long for evaluation. Almost all cases with less that 1 ft. of remaining jejunum died of inanition within one year. Those who had managed to live with remaining short segments of small intestine most often had at least 1½ ft. (45 cm.) of jejunum.

They wisely point out that the importance lies not in how much one resects but in how much small intestine remains. Measurements of a resected specimen may vary, depending on the person who does the measuring. If the specimen has been fixed in formalin, it will shrink and thus be shorter than when initially removed.

More recently, Uricchio and co-workers [3] have reported two more cases of extensive resection of the small intestine with very short segments of remaining small bowel. One patient is well, and the other survived for 15 months.

It is apparent from experimental and clinical studies that the tolerance of the experimental animal and of the human to resection of segments of intestine is often unpredictable. Much depends on the primary condition that necessitated resection, the length of intestine resected, and whether it was large or small intestine. The inherent ability of the person to compensate for intestinal loss may be another variable.

When one resects the right colon for neoplasm, the patient may experience a mild diarrhea that generally subsides in a few weeks. When a subtotal colectomy and ileosigmoidostomy is performed, the patient usually has some loose movements. This too is variable, and we recall two sisters who had all the colon except the terminal 15 cm. resected and an ileosigmoidostomy established for familial polyposis. The older sister has had four to six semiformed stools daily, while the younger girl has had no interference with her normal bowel routine. Apparently, the short segment of colon in the latter was able to take over completely the function of water absorption and fecal storage.

Colon resections interfere little with nutrition, while resections of segments of the small intestine are frequently followed by disturbances in nutrition. The small bowel carries digestion to completion and absorbs food products, while the colon absorbs water from the fecal stream and temporarily stores feces until elimination. In addition, small quantities of glucose and sucrose can be absorbed by the colon.[4] It might be said that the colon is an organ of convenience, while the small intestine is one of necessity.

It is common belief that removal of more than a third of the small intestine in a human will result in chronic nutritional insufficiency. If a patient is suffering from regional ileitis, resection of less than one third of the total length of the small intestine may be accompanied by profound deficiencies, due to lack of digestion and absorption of electrolytes, fats, and protein. Weight loss, loss of strength, anemia, and even tetany from lack of calcium absorption may be evident in excessive loss of small bowel.

Diets high in fat content often have an adverse effect if only a small length of small intestine remains, for such diets apparently contribute to excessive loss of calcium in the stools. Althausen and co-workers [5] have employed balance studies after extensive resections of the small intestine. They noted in one patient who had undergone a 90% resection of the small bowel that nutritional equilibrium was reached in 10 months. He has observed that it makes no difference whether one gives predigested foods or natural foods to patients who have undergone a massive resection. This would seem to lend further evidence to the importance of the small intestine in the absorption of food.

SUMMARY AND CONCLUSIONS

A case of resection of all but the proximal 8 in. of jejunum, the entire ileum, the ascending colon, and half the transverse colon is reported.

This person has managed to stabilize his weight and has remained in reasonably good health for 23 months after surgery.

A brief discussion, including similar cases previously reviewed, is presented.

Following extensive resection of small bowel it would seem advisable to avoid a high-fat diet, because of excessive loss of calcium in the stools when such a diet is employed in these persons.

347 West Barry St. (2).

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News and Comment

ANNOUNCEMENTS

American Trudeau Society Anniversary Meeting.—Three days of scientific papers, panel discussions, and special lectures on pulmonary diseases will mark the 50th anniversary meeting of the American Trudeau Society, medical section of the National Tuberculosis Association, beginning Monday, May 23, in Milwaukee, Wis. The meeting is being held in conjunction with the annual meeting of the NTA. All sessions will be in the Milwaukee Auditorium.

The chemotherapy of tuberculosis and other medical aspects of treatment, the surgical management of tuberculosis and related diseases, and current research will be discussed by specialists from all sections of the country.

Pan American Medical Association Congress.—The Tenth Inter-American Congress of the Pan American Medical Association will be held in Mexico City. The scientific sessions will begin on Monday, March 25, 1957, at 9:00 a. m., and will continue through March 31. The Congress will be held in sections covering all branches of medicine and surgery. There will be medical moving pictures, panel discussions, and scientific and technical exhibits. The Association has 42 Medical Sections, including the new "Section of General Practice."

Four days will be devoted to scientific sessions, and the next three days will be spent in sightseeing, with visits to Cuernavaca, Taxco, and Acapulco. Monday and Tuesday of the following week, medical meetings will be held in Guatemala City in conjunction with our local Chapter there.

A large number of physicians are expected to attend from all of the Latin American countries as well as from the United States and Canada.

The President of the Association is Dr. Pedro A. Gutiérrez Alfaro, Minister of Sanitation and Public Welfare of Venezuela, and the Executive Director is Dr. Joseph J. Eller, 745 Fifth Ave., New York 22.

International Archives of Allergy and Applied Immunology.—The *International Archives of Allergy and Applied Immunology,* beginning with the issue of January, 1955, will appear regularly on a monthly schedule. American authors should send their manuscripts for editorial consideration to the American editor-in-chief, Dr. William Kaufman, 540 Brooklawn Ave., Bridgeport, Conn.

American Heart Association Meeting.—The American Heart Association is holding its Annual Meeting this year in New Orleans, Oct. 22 through 26, and headquarters will be in the Jung Hotel. The Annual Scientific Sessions will be held Saturday, Oct. 22 through Monday, Oct. 24.

Those who wish to present a paper at one of the Scientific Sessions should submit an abstract, not exceeding 300 words, in duplicate, to the Medical Director, American Heart Association, 44 East 23rd St., New York 10, not later than July 1, 1955.

Research Fellowships in the Field of Multiple Sclerosis and Allied Diseases.—The National Multiple Sclerosis Society has established a limited number of fellowships to encourage promising students and scholars to enter the field of research related to multiple sclerosis and the demyelinating diseases. Fellowship candidates are free to elect a training institution and sponsor of their own choice. However, all candidates are urged to consider a training program looking toward preparation for a career of research in this broad general area of disease.

Types of Awards: Postdoctoral Research Fellowships. These awards will be made to qualified candidates holding a doctorate in medicine or in related fields and afford a basic stipend of $4000-$5000 per year based upon the academic and professional training of the applicant and the family dependency status involved.

Scholars. Appointment as a Scholar of the National Multiple Sclerosis Society will be made to qualified candidates holding a doctorate in medicine or in related fields and who have demon-

strated competence in biological investigation. This award will provide a stipend of $6000-$8000 per year based upon the academic record, professional training, and research attainments and interests of the applicant.

Term and Tenure of These Fellowships: These awards are usually made for one calendar year and may start any time within eight months of the date of notification of the award. One or two additional years of fellowship support may be requested; however, total tenure is not expected to exceed three years. In all cases additional years of support are dependent upon the terms of the original award and upon continued endorsement by the sponsor.

Application may be made at any time. Awards will be announced twice yearly—in June and in December. All prospective applicants must submit their applications and supporting documents to the NMSS on or before March 1 or September 1.

Sponsorship: Research Fellows and Scholars may undertake their training at any institution qualified to provide such training. It is the responsibility of the applicant to make all necessary arrangements for the conduct of his proposed training program both with his prospective sponsor and with the institution.

Concurrent Awards: These awards will not be made or continued concurrent with other fellowships except under unusual circumstances.

Clinical Training: Fellowships awarded by the National Multiple Sclerosis Society are not intended to support the routine clinical training of a resident where the primary aim of the resident is specialty board certification.

Teaching by Fellows or Scholars: Fellows or Scholars of the National Multiple Sclerosis Society are allowed to spend a reasonable amount of their time in teaching.

Grants of the Institution to Defray Fellowship Costs: Grants of up to $500 may be made to the sponsoring institution, upon application, as reimbursement for costs incurred by the institution incident to the training program. Tuition and other usual, related fees are chargeable against this grant.

Travel Reimbursement: A travel allowance of $150 will be allowed annually for travel from home to the sponsoring institution or to medical meetings.

Applications may be secured by writing to Harold R. Wainerdi, M.D., Medical Director, National Multiple Sclerosis Society, 270 Park Ave., New York 17.

Third Annual Antibiotics Symposium.—The Third Annual Symposium on Antibiotics, sponsored by the Food and Drug Administration, Division of Antibiotics, of the U. S. Department of Health, Education, and Welfare, with the journals *Antibiotics and Chemotherapy* and *Antibiotic Medicine*, will be held on Nov. 2, 3, and 4, 1955, in the Auditorium of the Department, 4th St. and Independence Ave., S. W., Washington, D. C.

So that contributors to the 1955 symposium will have ample time for preparation, the following outline is presented:

Submission of abstracts: An abstract in triplicate of no more than 200 words must be submitted no later than Sept. 21, 1955.

Submission of manuscripts: The original manuscript and one copy must be submitted by Oct. 3, 1955. Please note that this is a departure from requirements of the previous symposia. It will accomplish two objectives: (*a*) it will allow the program committee to make a better choice of material for presentation, and (*b*) it will allow earlier publication of the "Antibiotics Annual 1955-1956." Upon receipt of the manuscripts the committee will divide them into three categories: (1) those for presentation and publication, (2) those which will appear on the program by title and will be published but not presented, and (3) those which will appear by title on the program and only the abstracts published in the Annual.

Manuscripts must be new, previously unpublished material. They must be typewritten, double spaced, and only on one side of 8½ in. × 11 in. paper. No more than six illustrations should accompany each manuscript. Glossy photographs, no larger than 8½ in. × 11 in., of all illustrations should accompany the copies of the manuscript. Prints should be sufficiently clear to permit the making of engraver's cuts without retouching and to allow reduction to approximately ⅓ size. Bibliographies should conform to the style of the *Quarterly Cumulative Index Medicus*, published by the American Medical Association. Generic names of drugs should be used throughout the manuscript, except that the first time the drug is mentioned the trade name may be referred to in a footnote. Please submit manuscripts to Dr. Henry Welch, Director, Division of Antibiotics, Food and Drug Administration, U. S. Department of Health, Education, and Welfare, Washington 25, D. C.

All manuscripts will be published in English in book form under the title "Antibiotics Annual 1955-1956," by Medical Encyclopedia, Inc., 30 East 60th St., New York 22.

In addition to contributed papers, several outstanding investigators and clinicians will be invited to speak on timely and important topics related to their respective specialties prior to participation in special panel discussions.

Ames Awards Contest of American College of Gastroenterology.—The American College of Gastroenterology, in cooperation with the Ames Company, of Elkhart, Ind., takes pleasure in announcing the establishment of the Ames Award Contest for the best papers in Gastroenterology. There will be three classes of awards, as follows:

Fellows or residents of gastroenterology

First prize: $250.00, a certificate of merit, and a one-year subscription to *The American Journal of Gastroenterology*, official publication of the American College of Gastroenterology.

Second prize: $50.00, a certificate of merit, and a one-year subscription to *The American Journal of Gastroenterology*.

First or second year interns

First prize: $250.00, a certificate of merit, and a one-year subscription to *The American Journal of Gastroenterology*, official publication of the American College of Gastroenterology.

Second prize: $50.00, a certificate of merit, and a one-year subscription to *The American Journal of Gastroenterology*.

Best paper published

For the best paper published in *The American Journal of Gastroenterology*, during the twelve months ending June 30, 1955, for which no prize has been previously awarded, $100.00.

Rules and regulations: All papers submitted must represent original work in gastroenterology, must not have been previously published except for abstracts or short preliminary reports, and must not have been previously presented at any National meetings.

The contents of the papers can be clinical or basic science. Clinical papers must not be case records, but controlled clinical work.

The length of a paper is no criterion for originality or value.

All entries for the 1955 prizes, with the exception of those already published in *The American Journal of Gastroenterology*, must be typewritten in English, double-spaced on one side of the paper, and submitted in six copies.

The winning entries will be selected by the research committee of the American College of Gastroenterology, and the awards will be made at the Annual Convention Banquet of the College, to be held in Chicago, in October, 1955.

All papers selected for awards become the property of the American College of Gastroenterology, and the decision of the judges will be final. Should none of the papers submitted meet the standards set by the Committee, the Committee reserves the right to withhold the making of any award.

The recipients of the first prizes will present their papers in person at the Annual Meeting of the College.

All unpublished entries must be received no later than Sept. 1, 1955, and should be addressed to the Research Committee, American College of Gastroenterology, 33 West 60th St., New York 23.

Books

Smoking and Cancer: A Doctor's Report. By Alton Ochsner, M.D. Price, $2.00. Pp. 86, with 16 illustrations. Julian Messner, Inc., 8 West 40th St., New York 18, 1954.

In the great hubbub and confusion attending studies on cancer of the lung and its possible relationship to prolonged and excessive cigarette smoking and inhalation we have elegantly illustrated the reciprocal relationship between fact and passion, against the background of scandalous indifference of the multitudes making a livelihood from the tobacco business. Unfortunately Ochsner's book does little to clear the smoky fumes of opinion and dialectic enthusiastically adding to an impressive and growing body of data which fall in the category of probability. Instead of a dispassionate and factual approach to a problem of almost excessive complexity, there is profound faith in the already accepted conclusion. There is failure to look critically at the difference between testimony and evidence; failure to distinguish between evidence and proof; failure to reckon on the role of multiple causes in cancer of the lung, and, finally, assuming that there were no systematic but overlooked parallel developments, failure to recognize that parallels in incidence are not the same as cause and effect. And this is especially bad because the thesis presented probably is correct. It would be even worse if either the lay public or the medical public required rigorous logic or straight thinking in sorting out the vast hodge podge of fact and fancy which govern their conduct.

Now for some specific comments. First, in a book dealing with cancer it seems totally irrelevant to enter statistics connecting heart disease and smoking. This is especially true since it has never been shown that the relation of smoking to heart disease, assuming the apparent parallel increases are important, indicates that smoking causes heart disease, rather that people with certain physical and emotional drives and capacities also are habitual smokers, that people in certain occupations fraught with other hazards are more likely habitual smokers than those in the less strenuous crafts and trades. In short, it has not been shown that the person who is abstinent or moderate in smoking habits is not likewise moderate in his control over eating, drinking, working, and worrying. Unfortunately, to get an answer to this problem it will be necessary to take a group already divided along natural lines into heavy smokers and nonsmokers; divide each of those groups, making half of the nonsmokers heavy smokers and half of the heavy smokers nonsmokers, and follow them under controlled conditions for twenty years to see what happens. The fact that such studies are almost impossibly hard should not excuse us either in neglecting to do them or making the assumption that data collected with the utmost accuracy in the natural course of events can supply the missing answers. The danger of mistaking parallelism for cause and effect was graphically demonstrated to me early in my medical career by a great teacher who pointed out the nearly exact parallel increase in operations for appendicitis and the building of skyscrapers in New York City.

Perhaps the many stark statements which bring a wave of doubt to the mind of even the most casual skeptic may be explained by a statement on page 36 that the author is no longer a medical student. Further troubles are the boast on page 12 that preoperative diagnosis has been correct in 98% of the cases; the erroneous statement on page 27 that "while smoking one cigarette the women averaged a 33 per cent change in blood volume as compared with 19 per cent in men"; the great cloud of *non sequiturs* towards the end of chapter six relating to sterility in rabbits forced to breathe cigarette smoke; the assumption that nicotine is the specific cause of lesions found in rats; the confident acceptance of the relationship of sexual activity to lack of smoking, and the resort to a "German authority" not further indicated. An appeal to Benjamin Rush as authority calls to mind Cobbett's kindly observation that Rush's famous cure was "one of those great discoveries which have contributed to the depopulation of the earth." One loses contact with reality among the eddies and fumes of the author's befogged gyrations in the smoke-filled room of his mental processes which produce statements like "king-sized cigarettes make for king-sized cancer." The irony of this kind of book is that it is probable that its main thesis is correct. As a model of logic and exposition its focus is medieval.

Because the author of the above review anticipates that it may arouse adverse reaction he asks that it be signed so that responsibility is not cloaked by anonymity. Since honest opinion and forthright statement need no apology, the chief editor accedes to this request.

WILLIAM B. BEAN, M.D.

Lehrbuch der speziellen pathologischen Anatomie. By Dr. Eduard Kaufmann and Prof. Dr. Martin Staemmler. Price, DM 42. Pp. 320, with 150 illustrations. Walter de Gruyter & Co., Genthinerstrasse 13, Berlin W 35, 1954.

In medicine, as in other fields of endeavor, one finds certain books that have made their influence felt for extraordinarily long periods of time. For example, Virchow, in 1850, and Roessle, his successor as professor of pathology at the University of Berlin, in 1950, both acknowledged their debt to Cruveilhier's "Anatomie pathologique du corps humain," which was published in 1829.

"Das Lehrbuch der speziellen pathologischen Anatomie," by Eduard Kaufmann, late Professor of Pathology at the University of Göttingen, is such a book. Two whole generations of pathologists have grown up within arm's reach of this book and have acquired the habit of "look it up in Kaufmann" whenever they have encountered a difficult case. Rare, indeed, is the lesion that Kaufmann did not observe and describe.

Kaufmann published the first edition of his book in one volume in 1896 and the ninth and tenth edition, which was the last he himself revised, in two volumes in 1931-1940. Stanley Reimann translated the seventh and eighth editions into English in 1929. Now, Kaufmann's pupil and long-time assistant, Martin Staemmler, professor of pathology at Aachen, has edited the eleventh and twelfth edition. Volume 1, Part 1, which is the only portion of the new edition so far published, deals with diseases of the heart (pericardium, endocardium, and myocardium) and some of the diseases of arteries (hypertension, nonspecific inflammations, vasomotor disturbances, specific inflammation, and aneurysms). Staemmler wrote all of these sections. The second part of Volume 1, the publishers tell us, will contain sections on arterial hypoplasia, atrophy, hypertrophy, and neoplasia; diseases of veins; diseases of capillaries, and diseases of lymph vessels. In the third and final part of Volume 1, Prof. W. Doerr will write on congenital heart disease. Presumably subsequent volumes will deal with diseases of other organ systems.

In this new edition, Professor Staemmler has succeeded both in thoroughly modernizing the book and in preserving most of the individuality which Kaufmann gave it. Three important changes are at once apparent. Firstly, the original drawings, which were always a noteworthy feature of the book, have been largely replaced by excellent photographs of both gross and microscopic lesions. The editor obviously chose them with care, and the publishers have reproduced them with skill. Secondly, comprehensive and up-to-date bibliographies have been placed at the end of each section of the book. And thirdly, the text has been almost tripled—from 111 to 320 pages. Staemmler uses the same systematic treatment of the text that Kaufmann initiated in the first edition, but he has completely modernized its content. The sections on myocardial infarction, myocarditis, tumors, hypertrophy, and arteriosclerosis, for example, have been greatly expanded and contain fine discussions of modern views of the pathogenesis of these diseases. Among new topics in the book are Libman-Sacks endocarditis, parietal endocarditis, glycogen disease, disorders of the rhythm of the heart, hormonal disturbances, and irradiation effects. The only significant omission that I have discovered is an adequate consideration of endocardial sclerosis and idiopathic hypertrophy.

Old friends of Kaufmann's book will indeed be pleased with this new edition of it and will hasten to express their gratitude to Professor Staemmler for his magnificent labor of love.

Textbook of Pediatrics. Edited by W. E. Nelson, M.D. Ed. 6. Price, $15.00. Pp. 1581, with 487 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W.C. 2, 1954.

Here is a book which will be of great interest and utility to both pediatricians and internists. The reviewer, Dr. Frederick G. Scovel, Professor and Head of the Department of Internal Medicine, Christian Medical College, Ludhiana, Punjab, India, made the following comments in regard to the sections which interested him particularly.

P. S. R.

Parasitic diseases: The author presents a helpful and significant statement to the effect that freezing of meat destroys the encysted forms of Filaria, Taenia, and hydatid disease. The article

on flukes gives a good survey of the clinical forms. There is very little reference to the incidence of parasitic disease outside the U. S. The toxicity of centipede stings may be correctly stated for those in the U. S., but it is an understatement for those in Asia and Africa. Possibly the opposite is true for the assessment of scorpion bites.

Protozoan diseases: This is the first place that I have seen a definite statement that the sporozoites of plasmodia are deposited in the liver sinusoids, and I wonder if this is invariably the case. The remark that Plasmodium falciparum may damage the placenta and cause abortion should be studied here in India, where subtertian malaria is so prevalent in certain areas and where the incidence of neonatal malaria in infants born of malaria-infested mothers can be determined. Although the treatment of malaria without direct proof in blood smears is to be discouraged, as mentioned, yet it is often necessary in endemic areas where many patients are seen only after inadequate therapy. Although kala azar is not indigenous to the U. S., it is a pity this disease, so common in many parts of the world, is not mentioned.

Cardiovascular diseases: The introductory chapter, "The Heart and Circulation in Health and Disease," presents a fine summary and up-to-date references bridging the gap between pediatric and adult problems. This pertains especially to the use of cardiac catheterization in differential diagnosis, although there is no mention of the contribution of vectorcardiography. Very little mention is made of ballistocardiography, and reference is only made to the "Starr" Table, none to the electromagnetic ballistocardiograph. The discussion of coarctation of the aorta presents a timely emphasis on the importance of coexisting congenital defects. In fact each discussion on the various congenital cardiovascular defects mentions helpful and unusual diagnostic hints. The introduction to rheumatic fever was most thorough and the discussion of its management was more helpful than any previous discussion I have read.

Diseases of the blood: The introductory discussion on erythropoiesis seemed to be incomplete in its portrayal of the part played by the various factors. The term "anemia of chronic azotemia" is well chosen and would seem an improvement on the old diagnosis of "anemia of chronic nephritis." On page 959 the author mentions "only 12 cases of juvenile pernicious anemia have been reported," but no mention is given of the upper age limit. The suggestion on page 964 that iron be given between meals as phosphates and phytates in milk may inhibit absorption is important and new to most, I believe. That thrombocytosis and thrombotic phenomena follow splenectomy for hereditary spherocytosis is an important warning. Hemosiderosis complicating thalassemia is not emphasized by most authors. The section on erythroblastosis fetalis seemed to be almost too long to pick out the important parts. In the portion on leukemia mention was made that 90% of these cases in children are acute, but later it was mentioned only 2% have chronic myelogenous leukemia. No explanation of this discrepancy is given. The frequency of a low total white cell count in acute leukemia is emphasized here but not elsewhere.

Aspects of the Psychology of the Tuberculous. By Gordon F. Derner, Ph.D. Price, $3.50. Pp. 116. Paul B. Hoeber, Inc., 49 E. 33d St., New York 16, 1953.

In the preface to this monograph the author states he has attempted "an intensive study of the personality factors in persons with tuberculosis." As investigative tools he has used a series of clinical interviews and a variety of standard and specially devised psychologic tests. His initial comments that "psychological factors mediated through the autonomic nervous system and the body chemistry" may help constitute the "lowered resistance" which predisposes to this disease and that his data may help determine whether "there is a basic personality pattern for all tuberculous patients" are somewhat misleading and raise greater expectations than his study fulfills.

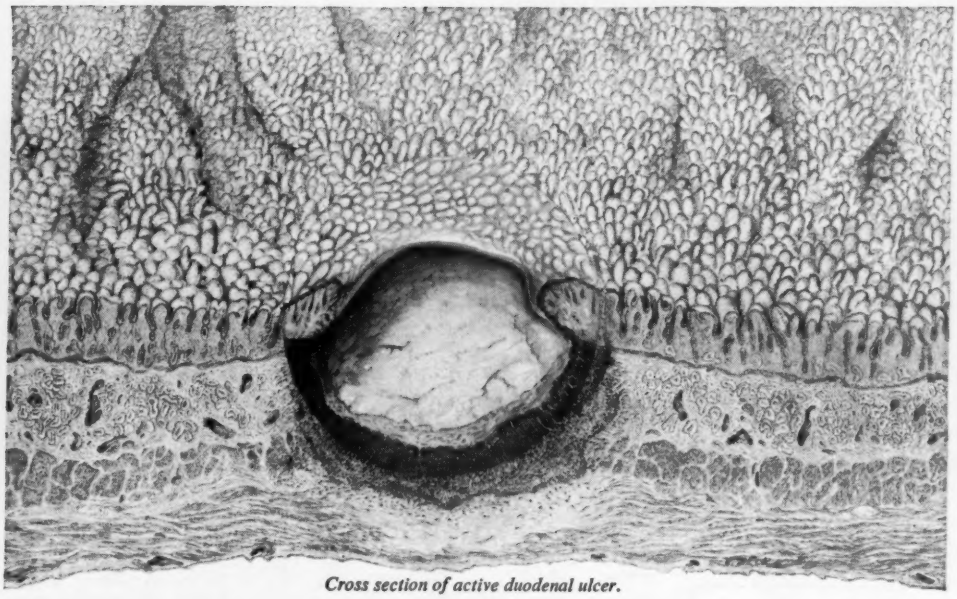
At the very outset it is evident that his study group of 32 subjects is too small for statistical purposes and, containing as it does 12 medical personnel (9 nurses and 3 physicians), is too unlike the average tuberculous population for its psychologic characteristics to have general application. Furthermore, there is little information on the premorbid personality patterns of these subjects and thus there are no baseline indices with which the study findings can be correlated. In consequence, his data are much less meaningful than might otherwise have been the case.

Apparently aware of these delimiting factors, the author has exercised judicious restraint in the presentation and discussion of his results. These are restricted to the reaction of the patient to his disease and reaffirm rather well known observations which, nevertheless, warrant reemphasis. In essence, he indicates that the diagnosis of tuberculosis is an emotionally trau-

matic event usually evoking a response of fear, apprehension, and depression; that the actual and potential consequences of this disease are everpresent and uppermost in the patient's thoughts; that most lay patients have little understanding of tuberculosis and are often unnecessarily alarmed by misinformation from family, friends, and fellow patients, and that there appears to be "no unique tuberculosis personality." His specially designed procedure for the detection of "spes phthisica" provides no evidence to support the prevalent belief that tuberculous subjects commonly manifest an inappropriate euphoria. This is probably a valid observation but will require substantiation on a more typical group of subjects.

The implications drawn from this study by the author are valid but, in the light of his earlier comments, are somewhat anticlimactic and so nonspecific as to apply with equal pertinence to most chronic diseases. In brief, he emphasizes the importance of the holistic therapeutic approach—the consideration and treatment of the total patient, not merely his disease.

This monograph is well written and attractively published. It will be of interest to psychologists, psychiatrists, and phthisiologists. Unfortunately, the basic defects handicap its elucidation of those "aspects of the psychology of the tuberculous" with which these workers are most importantly concerned.



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2. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, Gastroenterology *25*:416 (Nov.) 1953.

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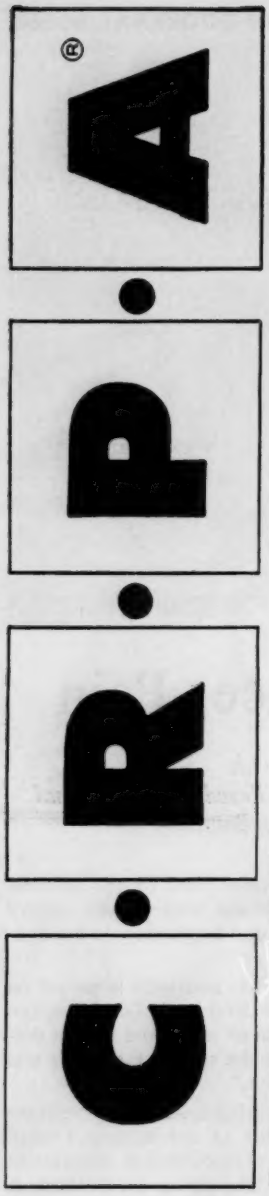

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1. Wood, H. F., and McCarty, M.: Am. J. Med. *17*:768 (Dec.) 1954. 2. Adams, F. H.: J.A.M.A. *156*:1319 (Dec. 4) 1954. 3. Stollerman, G. H., et al.: Am. J. Med. *15*:645 (Nov.) 1953. 4. McEwen, C.: M. Clin. North America (Mar.) 1955, to be published. 5. Elster, S. K.; Wood, H. F., and Seely, R. D.: Am. J. Med. *17*:826 (Dec.) 1954.

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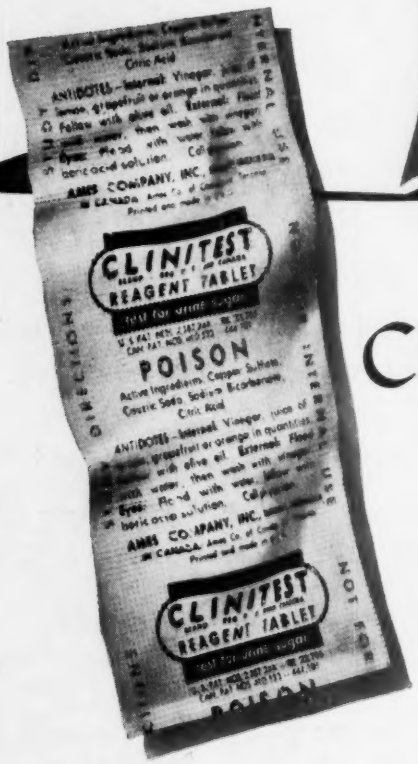

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